RISK OF MORTALITY IN SECONDARY MENTAL HEALTH TREATMENT FOR OPIOID USE DISORDER

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RISK OF MORTALITY IN SECONDARY MENTAL HEALTH TREATMENT FOR OPIOID USE DISORDER

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TABLE OF CONTENTS

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DECLARATION

This declaration is to certify that

(i) the thesis contains only my original work,

(ii) due acknowledgement has been made in the text to all other material used,

(iii) the thesis is less than 100,000 words in length, exclusive of bibliography and appendices.

Karolina M. Bogdanowicz

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

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ABSTRACT

This thesis utilizes anonymized patient health records from one of the largest mental health service providers in Europe and explores mortality risk factors, at both patient-level and service-level, in individuals with opioid use disorder (OUD) enrolled in secondary drug and alcohol treatment. The thesis explores associations between psychological wellbeing, comorbid diagnosis of personality disorder (PD), serious mental illness (SMI) and alcohol use disorder (AUD), in relation to mortality in opioid dependence. Specific risk situations in time and context are also explored, with investigations of clustering of deaths in the period immediately after transfer of patients and their care and after end of opioid substitution treatment (OST) in a cohort of opioid dependent individuals in specialist addiction treatment. The thesis also investigates if routine brief risk assessments given to OUD patients can predict all-cause or cause specific mortality and determine if these risks may be modified by admission to services.

LIST OF ABBREVIATIONS

AUD	ALCOHOL USE DISORDER
BBV	BLOOD BORNE VIRUS
BRC	BIOMEDICAL RESEARCH CENTRE
BRSA-A	BRIEF RISK SCREEN ASSESSMENT – ADDICTIONS
CAG	CLINICAL ACADEMIC GROUP
CDAT	COMMUNITY DRUG AND ALCOHOL TREATMENT
CMR	CRUDE MORTALITY RATIO
CNS	CENTRAL NERVOUS SYSTEM
CRIS	CLINICAL RECORDS INTERACTIVE SEARCH
CSV	COMMA-SEPARATED VALUE
CSEW	CRIME SURVEY FOR ENGLAND AND WALES
DALY	DISABILITY ADJUSTED LIFE YEAR
DOH	DEPARTMENT OF HEALTH
DRD	DRUG RELATED DEATH
DSM	DIAGNOSTIC AND STATISTICAL MANUAL FOR MENTAL DISORDERS
EHR	ELECTRONIC HEALTH RECORDS
EMCDDA	EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION
EPJS	ELECTRONIC PATIENT JOURNEY SYSTEM
GATE	GENERAL ARCHITECTURE FOR TEXT ENGINEERING
GBD	GLOBAL BURDEN OF DISEASE
GP	GENERAL PRACTICE
HCV	HCV HEPATITIS C VIRUS
HES	HOSPITAL EPISODE STATISTICS
HIV	HUMAN IMMUNODEFICIENCY VIRUS
HONOS	HEALTH OF THE NATION OUTCOME SCALE
HR	HAZARD RATIO
ICD-10	INTERNATIONAL CLASSIFICATION OF DISEASES (10^{TH} EDITION)
LAS	LONDON AMBULANCE SERVICE
LSOA	LOWER SUPER OUTPUT AREA
MMSE	MINI-MENTAL STATE EXAMINATION
NDTMS	NATIONAL DRUG TREATMENT MONITORING SYSTEM

NHS	National Health Service
NIHR	National Institute for Health Research
NLP	Natural language processing
NTA	National Treatment Agency
OD	Overdose
ONS	Office for National Statistics
OST	Opioid substitution therapy
OUD	Opioid use disorder
PD	Personality disorder
PHE	Public Health England
PWID	People who inject drugs
PY	Person-years
RR	Rate ratio
SHR	Sub-distribution hazard ratio
SLAM	South London and Maudsley NHS Foundation Trust
SMI	Severe mental illness
SMR	Standardized mortality ratio
SOCA	Serious Organized Crime Agency
SQL	Structured query language
TOP	Treatment outcome profile
UNDOC	United Nations Office on Drug and Crime
WHO	World Health Organization
YLL	Years life lost due to premature mortality

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1 INTRODUCTION

1.1 STATEMENT OF THE PROBLEM INVESTIGATED IN THIS THESIS

In England and Wales, deaths involving heroin and/or morphine doubled in the last three years and are now the highest on record (ONS, 2016). Despite the relatively rare prevalence of opioid use, compared with other illicit substances (CSEW, 2015), there were more than 6000 drug-related deaths involving opioids in the last 5 years (ONS, 2016). Enrollment in treatment is the single most effective road to recovery and to minimize harms associated with opiate drug-use during this journey (Darke et al., 2000; Davidson et al., 2003; McGregor et al., 1998; Pierce et al., 2016). However, certain mortality risks within OUD treatment exist and these need careful exploration and interpretation.

This thesis utilized anonymizes patient health records from one of the largest mental health service providers in Europe and explored mortality risk factors, at both patient-level and service-level, in individuals with OUD enrolled in secondary drug and alcohol treatment. The aims of the thesis are:

1. To explore associations between psychological wellbeing, comorbid diagnosis of PD, SMI and AUD, in relation to all-cause and cause-specific mortality in opioid dependence.
2. To determine if addiction-specific, routine brief risk assessments given to OUD patients can predict all-cause or cause specific mortality. Also, to determine if these risks may be modified by admission to services.
3. To investigate clustering of deaths, especially fatal overdoses, in the period immediately after transfer of patients and their care, and after end of OST in a cohort of opioid dependent individuals in specialist addiction treatment.

4. To investigate the associations between planned OST cessation, unplanned OST cessation and transfer of patient and their care with arranged continuation of OST, in relation to all-cause and cause-specific mortality in opioid dependence with adjustment for potential confounders.

The findings of this thesis might provide evidence of the burden of opioid use disorder in secondary mental health services and the general population. The specific aims in this thesis might identify specific areas of risks with a direct clinical and policy implications.

1.2 DEFINITIONS

1.2.1 HEROIN, OPIATES AND OPIOIDS

Heroin, a crude preparation of diamorphine, is a semisynthetic product obtained by acetylation of morphine, which occurs as a natural product in opium, the dried latex of certain poppy species (e.g. *Papaver somniferum*) (Darke, 2011; European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2015); King, 2009). Diamorphine is a narcotic analgesic used in the treatment of severe pain. Illicit heroin may be smoked, inhaled as a sublimate, or dissolved with a weak acid and injected. Whilst opium has been smoked since historical times, diamorphine was first synthesised in the late nineteenth century. Diamorphine is 2–3 times more potent than morphine (EMCDDA, 2015).

The opioids are a class of drugs that include the natural products from the opium poppy and synthetic compounds derived from it. The term describes any of the narcotic opioid alkaloids found as natural products in the opium poppy plant, as well as many semi-synthetic chemical derivatives (EMCDDA, 2010). In addition to heroin, the class includes drugs such as morphine, codeine, methadone, oxycodone and fentanyl. Although the term ‘opiate’ is often used as a synonym for opioid, this term is properly limited to only the natural alkaloids from in the resin of the opium poppy (Darke, 2011; King, 2009). This thesis concentrates on individuals who misuse opioids. Although heroin is the primary problematic substance, the cohort studied here does not exclude the misuse of other opioids.

One of the primary clinical characteristics of opioids is that they produce analgesia. Opioids act as agonists for a group of neuro-receptors that are normally acted upon by

endorphins, the body's endogenous opioids (Berridge, 2009). Apart from analgesia, opioids induce drowsiness and sleep, and produce a sense of euphoria and detachment. The onset of these effects can be very rapid. Following heroin injection, diamorphine rapidly crosses the blood-brain barrier within approximately 20 seconds (which is one of the major reasons why injection is often the favoured choice of route of administration), and includes feelings of warmth and pleasure followed by a long period of sedation (Darke, 2011). The major clinically significant negative effect of the opioids is that they are central nervous system (CNS) respiratory depressants (Karch, 2009). Respiration rates are suppressed, even amongst the tolerant and, in overdose, may decline to just four breaths per minute, if the person still lives. Death is usually due to respiratory failure, although cardiac arrests may occur due to myocardial oxygen deprivation (Goodman & Gilman, 1996).

1.2.2 OPIOID USE DISORDER

The cohort analysed in this thesis consists of patients diagnosed with an opioid use disorder (OUD) in accordance with the 10th edition of the International Classification of Diseases (ICD-10) (World Health Organisation [WHO], 1993). The ICD-10 classification of mental and behavioural disorders due to use of opioids is categorized into three pathological syndromes: intoxication, dependence syndrome and withdrawal state. Detailed diagnostic criteria for each of the syndromes are presented in Table 1.1.

Of all the drug classes, heroin is second in dependence liability (after tobacco), with approximately one in four who use heroin developing dependence upon the drug, and with no gender differences in that respect (Anthony et al., 1994). Higher rates of use

and transitions to dependence (1 in 2) were found in combat setting (Robins, 1993); and with injecting of heroin being associated with the highest level of dependence (Gossop et al., 1992).

Table 1.1 ICD-10 diagnostic criteria for Mental and Behavioral Disorders due to use of opioids (WHO, 1993)

OPIOID INTOXICATION
1) There must be clear evidence of psychoactive substance at sufficiently high dose levels. 2) There must be symptoms or signs of intoxication, of sufficient severity to produce disturbances in the level of consciousness, cognition, perception, affect, or behaviour that are of clinical importance. 3) These symptoms and signs cannot be accounted for by a medical disorder unrelated to substance use disorder. 4) There must be dysfunctional behaviour as evidenced by the presence of at least 1 among the following: apathy, sedation, disinhibition, psychomotor retardation, impaired attention, impaired judgement, interference with personal functioning. 5) At least 1 of the following signs, such as drowsiness, slurred speech, pupillary constriction, decreased level of consciousness, must be present. In severe acute opioid intoxication, respiratory depression, hypotension, and hypothermia will be present.
OPIOID DEPENDENCE SYNDROME
Three or more of the following manifestations should have occurred together for at least 1 month, or if persists for <1 month, should have occurred together repeatedly within a 12-month period: 1) A strong desire or sense of compulsion to take opioids 2) Impaired capacity to control substance-taking behaviour in terms of its onset, termination, or levels of use 3) A physiological withdrawal state when use is reduced or ceased, or use of same substance with intention of relieving or avoiding withdrawal symptoms 4) Tolerance: marked increase in amount with marked decrease in effect 5) Preoccupation with opioid use: more time spent to obtain, take, or recover from effects of substance 6) Persistent opioid use despite clear evidence of harmful consequences.
OPIOID WITHDRAWAL STATE
1) There must be clear evidence of recent cessation or reduction of opioid use after repeated, and usually prolonged and/or high-dose, use of that substance. 2) Symptoms and signs compatible with known features of withdrawal state. Any 3 of the following signs must be present for opioid withdrawal state: craving for opioid drug, rhinorrhoea or sneezing, lacrimation, muscle aches or cramps, abdominal cramps, nausea or vomiting, diarrhoea, pupillary dilation, piloerection, recurrent chills, tachycardia, hypertension, yawning, or restless sleep. 3) All these symptoms and signs cannot be accounted for by a medical disorder unrelated to opioid use disorder.

1.2.3 OPIOID SUBSTITUTION THERAPY

Opioid substitution therapy (OST) with methadone, buprenorphine (commercially marketed as Subutex or Suboxone [buprenorphine/naloxone]) is currently the most effective and approved treatment to achieve abstinence from heroi, and to avoid or minimize harm associated with drug use (Strang et al., 2012), although some risks associated with OST have been highlighted in the literature (e.g. Degenhardt et al., 2014a), as will be explored in further chapters.

These long-acting opioids provide relief from craving and withdrawal symptoms and allow the patient to escape the domination of illicit opioids over the rest of their lives. The large amounts of time previously spent getting money to buy the drug, being intoxicated, or withdrawing is now freed up by the use of a single daily dose of supervised, pure and long-acting opioid (Darke, 2011).

Once stability is achieved and sustained the opioid maintenance dose can be slowly reduced, and in stable cases, weaned off altogether. Maintenance opioid treatment of heroin dependence results in 70% reduction in heroin use and improved treatment retention compared with non pharmacological treatments, but with substantial dropout from treatment with only about 40%-50% of patients remaining in treatment at six months (Mattick et al., 2014; Connock, 2007; The National Institute for Health and Clinical Excellence [NICE], 2007). It avoids the multiple complications associated with injecting drug use, substantially reduces criminal activity and enables re-engagement in routine life (Darke, 2011).

Public Health England's (PHE, 2015) report states that the number of people in treatment for opiate misuse has been steadily declining in recent years from 170,032 in 2009/10 to 152,964 in 2014/15. This is particularly the case for younger people (under 25) where the number of people presenting for treatment for opiate misuse has declined by 60% between 2009/10 and 2014/15. In contrast, since 2009/10, the number of opiate users aged 40 and over starting treatment has risen by 21%. This ageing cohort of heroin users often have a range of complex physical illnesses as a result of long-term drug use, which may make them particularly vulnerable (Office for National Statistics [ONS], 2015; Pierce et al., 2015).

1.3 EPIDEMIOLOGY OF OPIOID USE

1.3.1 HISTORICAL USE OF OPIOIDS

Despite difficulties in interpreting ancient writings and archaeological data, a picture of opium use in antiquity does emerge from them. The Sumerians (Iraq) cultivated poppies and isolated opium from their seed capsules at the end of the third millennium B.C. It appears that opium spread from Sumeria to the remainder of the old world (Brownstein, 1993). Most authors agree that, as early as the eighth century A.D., Arab traders brought opium to India (Dwarakanath, 1965) and China (Fort, 1965) and that between the tenth and thirteenth centuries opium made its way from Asia Minor to all parts of Europe. After the invention of the hypodermic syringe and hollow needle in the 1850s, morphine began to be used for minor surgical procedures, for postoperative and chronic pain, and as an adjunct to general anaesthetics (Brownstein, 1993).

Throughout the 19th century opium could be purchased directly from chemists and even grocers (Berridge, 2009; Berridge & Mars, 2004; Strang, 1990). Opium imports rose from 17,302 pounds in 1827 to 61,269 by 1859 (London, 2005). Britain became a major world supplier of narcotics through its colonial possessions and only relinquished this role after World War I. In 1868, the Poisons and Pharmacy Act was passed, which restricted the right to supply opium to health professionals and required precise labeling and recording (Berridge, 2009). Patent medicines were restricted towards the end of the century, and in 1908, opium was placed on the Poisons List. During the five years after 1868, accidental opiate poisonings fell by 26%, and dropped a further 20% following the 1908 Act (London, 2005)

In the early decades of the 20th century, opiate use was rare, and in the 1920s, fewer than a hundred cases were prosecuted each year under the Dangerous Drugs Act (Berridge & Edwards, 1981; London, 2005). Heroin was unusual and half the cases were Chinese men using opium. Of morphine users, two-thirds were doctors, nurses, or pharmacists, and most offenses were for forged prescriptions. The illicit opiate trade was small, and the management of opiate addiction was left largely in the hands of the medical profession (Berridge & Edwards, 1981; London, 2005). Concern mounted in the 1960s when the profile shifted toward marginalized young men using heroin in a way that was more akin to the situation in the United States. The number of known heroin addicts grew from around 50 in 1957 to almost 1300 a decade later, finally reaching 20,000 in 1996, half of them new to treatment services (Ghodse, 2002). There has been a steady rise in opiate use, with consumption spreading from metropolitan centres into rural communities and notable surges in response to international events altering the illicit chain of supply (United Nations on Drugs and Crime [UNODC], 2015).

1.3.2 CURRENT PREVALENCE OF OPIOID USE

Opioid use is a global problem. It was estimated that, worldwide, between 26 and 36 million people aged between 15 and 64 used opioids in 2010 (UNODC, 2012), which translates to between 0.6% and 0.8% of the global population. Rates appeared to be highest per capita in Europe (0.6%-0.7%), followed by Americas and Oceania (0.4%), Africa (0.2%-0.5%) and Asia (0.3%-0.5%). Nearly half, or between 13 million and 21 million, of global opioid use constitutes the use of opiates, particularly heroin (UNODC, 2012). Recent use estimates in some major heroin markets include the

United Kingdom (0.1%), the United States (0.2%) and Australia (0.2%) (Darke, 2011).

Approximately 10.4 million people aged 15 years and older in 1990 were opioid-dependent and 15.5 million people in 2010, according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) - the largest and most comprehensive effort to date to measure epidemiological levels and trends worldwide (Degenhardt et al., 2014b).

The largest absolute numbers of opioid-dependent people in 2010 were estimated to be in South Asia (4.3 million people), East Asia (2.2 million), North Africa and the Middle East (1.37 million) and western Europe (1.32 million) (Degenhardt et al., 2014b). However, the underlying methodology, as defined in DSM-IV (4th edition of the Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association [APA], 2000), for these estimates are restricted to dependence and exclude abuse or harmful use (as defined in ICD-10), therefore are likely to underestimate the real burden of drug use.

In England and Wales, only 0.1% of responders in the recent Crime Survey in England and Wales (CSEW, 2015) indicated the use of opioids, which is relatively rare when compared to other illicit drugs (presented in Table 1.2). However, as a household survey, the CSEW does not cover groups such as the homeless, or those living in institutions such as prisons, therefore, are likely to underestimate the burden of opioid use within England and Wales. The PHE, a more accurate estimate (but only reporting figures for opiates and/or crack cocaine) reports that more than 250,000 people in England used opiates in 2011/12 (PHE, 2013)

Nonetheless, despite differences in prevalence reporting, more than 150,000 people who were using opiates were in addiction treatment (between 2014-15), which constitutes an overwhelming majority of all clients in contact with addiction treatment services (79%) (PHE, 2015).

1.4 WHY MORTALITY AMONG OPIOID-USERS MATTERS

1.4.1 ETHICAL RESPONSIBILITY

The prevention of premature death is generally considered uncontroversial and the same approach should be applied for drug-related harm. Literature demonstrates several clear precursors for increased risk of opioid use and opioid dependence. In particular, the development of problematic drug-use has been strongly associated with "shattered childhood" (Rosow & Lauritzen, 2001), parental psychopathology, parental drug and alcohol problems, early loss of parents, and childhood sexual and physical abuse (Rossow & Lauritzen, 2001). The development of opioid-dependence is therefore not a random occurrence.

Consistent with this view, levels of psychopathology such as major depression and or personality disorders are high amongst opioid-users (Drake & Ross, 1997; Teesson et al., 2005) (discussed in more detail in Chapter 2 and 4). Therefore, the majority of problematic drug users come from backgrounds that increase their risk of serious psychopathology and of drug dependence.

Furthermore, the majority of drug-related fatalities occur amongst dependent drug users (Darke et al., 2007). Opioid dependence is a well-recognized psychiatric diagnosis and the syndrome includes both physical and psychological symptoms. The core feature of opioid dependence is a loss of control over use of the drug (as specified earlier) (WHO, 1993; APA, 2000). The person may be physically dependent on the drug, experiencing drug tolerance and withdrawal symptoms, and continue to use despite repeated efforts at abstinence (Darke, 2011). Therefore, drug-use should

not be regarded as a choice when the person had been diagnosed as having lost control over their drug use.

It is also unclear how drug-related deaths could be distinguished from other fatalities that are universally deemed worthy of clinical intervention - for example, tobacco, alcohol-related disease or suicide. Suicide itself, as will be discussed further below and in Chapter 4, is a major cause of death amongst opioid users (Darke & Ross, 2002).

Finally, the typical onset of illicit drug use occurs in the teenage years (Degenhardt et al., 2000), prior to the person becoming an adult deemed ethically or legally responsible for their own actions. While the person may die as an adult, the dependence that leads to his or her death, typically, was acquired as a minor, particularly when adverse events in childhood have occurred.

1.4.2 COSTS TO SOCIETY

Opioid use places a substantial cost burden upon societies. For example, there is a strong association between dependent drug use and crime (Flynn et al, 2003). This association, however, is between drug use and crimes committed by dependent drug users to acquire money to purchase drugs (Darke, 2011; Flynn et al, 2003). Importantly, the frequency of acquisitive crime has been demonstrated to co-vary with the frequency of illicit drug use (Flynn et al., 2003) and with criminal behaviours declining markedly as a result of drug-treatment programs (Hardwood, 1990).

In addition to crime, injecting of drugs, especially opioids, is strongly associated with disease and disease transmission. The sharing of used injecting equipment is a major transmission factor for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (Karch, 2002), as discussed further below. There are also a range of other pathologies associated with drug use, including cardiovascular disease, pulmonary disease, renal complications and neuropathology (Pierce et al., 2015). As with crime, however, the health of illicit drug users improves substantially after entering drug-treatment programs (Gossop et al., 2002).

While there are substantial costs associated with illicit drug use, the deaths of large numbers of drug users also imposes a substantial cost upon society. As will be seen in later chapters, the average age of death amongst illicit drug users is around 35 years (Gossop et al., 2002; Stebnacka, 2010). Given the relatively young age of such deaths, there is considerable lost productivity due to truncated lifespan.

1.4.3 NATURAL HISTORY OF DRUG USE

Illicit drug use typically commences in the mid-teenage years, peaks in the 20-30-year age group, and declines sharply in older age groups (Chen & Kendel, 1995). The natural history of illicit drug use is therefore skewed toward the younger years. A person may use drugs in their 20s or 30s, but he or she may cease to do so in later years. The highest risk of illicit drug use, and of mortality, is therefore focused over a relatively short period of time in one's life. Many dependent users may be seen to "mature out" of drug use, although this may take considerable time (Flynn et al., 2003; Darke et al., 2007). Drug-treatment programs produce substantial improvements in the psychological profile of dependent users (Mattick et al., 2009;

2014). A dependent user may be a high-risk person who imposes a societal burden, they may not however remain a dependent user or continue to impose such burden.

1.4.4 FAMILIES OF DRUG USERS

Although not directly discussed in this thesis, the impact of deaths upon the families of opioid users must also be considered in this section. The loss of loved ones through drug use matters greatly to the families of drug users (Strang et al., 2008; Williams et al., 2014). In considering whether drug use mortality is a legitimate matter of concern, the drug user must not be seen in isolation. The death of a drug user does not only affect the user themselves, but also those surrounding them (Strang et al., 2008). The most salient issue here clearly concerns the children of drug users. As mentioned earlier, early parental loss is associated with increased risk of the development of subsequent psychopathology, as well as increased risk of drug dependence and of suicide (Rossow & Lauritzen, 2001).

1.5 MORTALITY RATES AND THE BURDEN OF DISEASE

According to the GBD (Degenhardt et al., 2014b) a total of 9.2 million DALYs (disability-adjusted life years) were attributed to opioid dependence in 2010: 0.37% of global DALYs. The GBD is the most comprehensive worldwide observational epidemiological study to date, which describes mortality and morbidity from major diseases, injuries and risk factors to health at global, national and regional levels.

This burden was estimated to have increased markedly over time, with increased prevalence of opioid dependence the predominant driver of increased burden, rather than changes in the age structure or size of the global population. The GBD concluded that opioid dependence is an increasing source of global disease burden, with substantial regional variations; and also with striking variations in the contribution made by YLLs (years of life lost due to premature mortality) to regional-level opioid burden. In particular, North America, Eastern Europe and Southern sub-Saharan Africa had greater than 50% of DALYs attributable to YLLs; possibly due to limited access to interventions that reduce mortality (e.g. OST, needle exchange, HIV/HCV medication).

In England and Wales, deaths involving heroin and/or morphine (heroin is metabolised as morphine and hence, the presence morphine often indicates heroin use) doubled in the last three years, from 579 in 2012 to 1,201 in 2015, and are now the highest on record (ONS, 2016).

Despite relatively rare prevalence of opioid use, compared with other illicit substances (CSEW, 2015), there were more than 6000 drug-related deaths involving opioids in the last 5 years (ONS, 2016) (presented in Table 1.2).

Between 2008 and 2012, the ONS noted a decline in heroin/morphine related deaths, with a particularly sharp fall between 2009 and 2011 (ONS, 2016). This most recent reversal means that the mortality rate in 2015 was the highest since records began in 1993 and now exceeds the previous peak in 2008, which occurred before the "heroin drought" in 2010/11 (Serious Organized Crime Agency [SOCA], 2011, 2012, 2013, 2014). Heroin and methadone continuously form the largest proportion of opioid-related deaths (presented in Figure 1.1) (PHE, 2016).

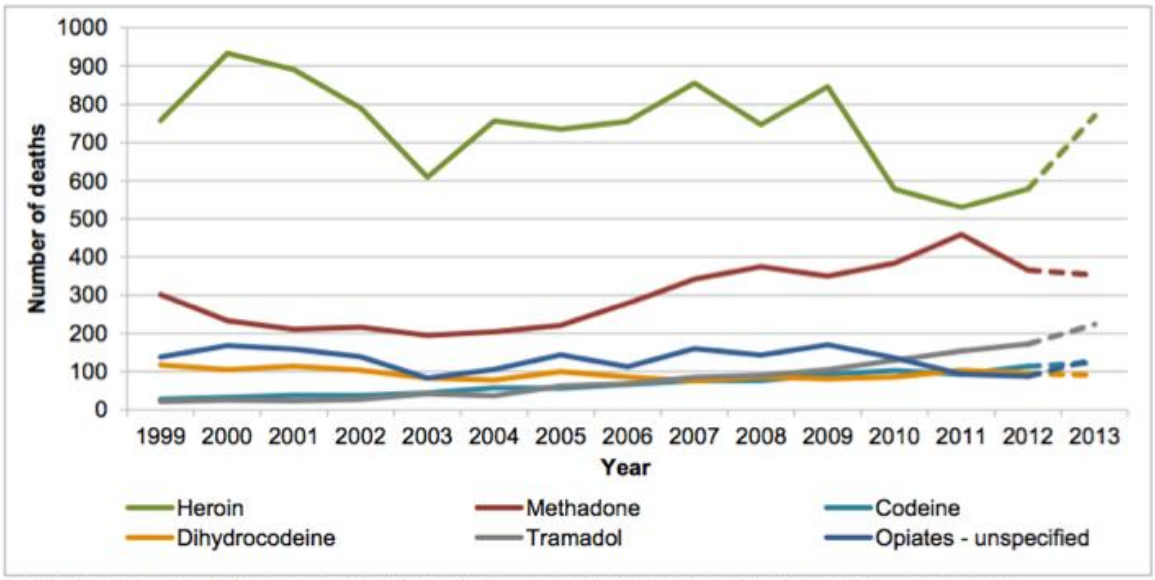
Increases in the number of drug related deaths (DRD), particularly those involving heroin/morphine, were seen across all ages between 2014 and 2015, with the biggest rises occurring in those aged 50 to 69. Both the male and female mortality rate for deaths involving heroin/morphine increased in 2015, but the increase was sharper in males (31% compared with 9%) (PHE, 2016). Different DRD trends between gender are seen over time; for example, the sharp fall between 2009 and 2011 was only seen in males, while female rates remained stable during this time. These gender differences may be partially explained by the fact that a greater proportion of female deaths involving heroin/morphine are suicides (rather than accidental overdoses), which are less likely to be affected by changes in the purity of heroin (PHE, 2016) (see cause specific mortality below).

Table 1.2 Drug related deaths and prevalence of drug use in England and Wales.

Drug	Prevalence of use*	Number of deaths in the last 5 years±
Cannabis	6.7%	81
Cocaine	2.4%	987
MDMA/Ecstasy	1.7%	194
Opiates (heroin, morphine, methadone)	0.1%	**6250**

*Prevalence of use in general population aged 16-59, reported in 2014/215 (CSEW, 2015)
±Deaths related to drug poisoning in England and Wales in 2015(ONS, 2016)

Figure 1.1 Mentions of opiates, by year (PHE, 2016).



Note: Dotted line for 2013 reflects partially incomplete data and 2014 data is omitted due to being substantially incomplete

1.6 CAUSES OF DEATH

1.6.1 OVERDOSE

By the age of 50, approximately half of any cohort of opioid users will have died (Degenhardt et al., 2011), although there will be geographical variation to this estimate depending on, for example, availability of treatment, availability of harm reduction intervention and the prevalence of BBV. Nonetheless, as will be seen in later chapters, overdose (OD) is the most common cause of death (Brugal et al., 2005; Darke & Hall, 2003; Warner-Smith et al., 2001). Worldwide, an estimated 69,000 people die from opioid overdose (accidental or deliberate) each year (WHO, 2014). In England and Wales, more than 1700 deaths registered in 2014 (53% of all deaths from drug poisoning) involved an opiate drug (ONS, 2015).

Existing literature has identified several prominent overdose risk factors. The typical overdose fatality occurs in a long-term, dependent, drug-injecting user in their 30s or older (Pierce et al., 2015; Stebnacka et al., 2010). Overdoses overwhelmingly occur when the person is not enrolled in drug treatment (Darke et al., 2000; Davidson et al., 2003; Pierce et al., 2016). An important feature to be noted (and one which this thesis considers) is that while the "picture" here is of high heroin tolerance due to frequent use, there are occasions of reduced tolerance that increase transient overdose risk. This aspect is explored in the next chapter and more fully in Chapters 6-7, where reinstatement of use after a period of abstinence, such as post-detoxification with cessation of OST or after prison release, is associated with substantially increased mortality risk (Cornish et al., 2010; Cousins et al., 2016; Farrell & Marsden, 2008; Strang et al., 2003).

Concomitant use of other CNS depressants, such as alcohol and benzodiazepines, has also been identified as one of the most prominent overdose risks, due to the potentiation of the respiratory depressant effects of heroin (Darke et al., 2007; Jones et al., 2012). This risk also extends to deaths attributed to other opioids such as methadone and buprenorphine (Oliver et al., 2007). By far the most common substance detected is alcohol, presented in half or more of overdose cases (Darke et al., 2010). Concomitant alcohol use and overdose mortality is also explored in more detail below and in Chapter 4.

The route of heroin administration is also of importance. In particular, injecting is associated with the highest risk for overdose, due to delivery of a bolus to the brain (Gossop et al, 1996; Milloy et al., 2008; Pierce et al., 2016; Powis et al., 1999).

Finally, non-fatal overdoses are of clinical significance because a history of overdose strongly predicts future overdoses, thus those who overdose are more likely to do so again (Darke et al., 1996; McGregor et al., 1998; Powis et al., 1999; Kerr et al., 2007). Non-fatal overdose often includes prolonged unconsciousness and is associated with a range of serious health risks, such as pulmonary oedema, bronchopneumonia, 'crush syndrome' (rhabdomyolysis), renal failure, cognitive impairment and traumatic injuries sustained during an overdose (Warner-Smith et al., 2001, 2002). It is estimated that the proportion of heroin overdoses that result in death is between 2% and 4% (Darke et al., 2003). Thus, for every fatal overdose, 25-50 'near-misses' might be expected.

Studies consistently report that one- to two-thirds of users have overdosed, usually on multiple occasions, with annual rates of 15%-25% (Britton et al, 2010; Wines et al.,

2007). While non-fatal overdoses are certainly a matter of importance, I was unable to explore non-fatal overdoses in these thesis due to the methodological constraints described in Chapter 3.

1.6.2 SUICIDE

It is estimated that heroin dependence is associated with a completed suicide risk 14 times that of the general population (Harris & Barraclough, 1997; Wilcox et al., 2004). Studies report that 5–10% of heroin user deaths are due to suicide (Maxwell et al., 2005, Stenbacka et al., 2010).

A range of psychopathology has been associated with suicide, with mood disorders having a particularly strong relationship, where risk increases 20-fold (Harris & Barraclough, 1997, Wilcox et al., 2004). Similarly, a history of family dysfunction, social isolation and disadvantage are also associated with higher suicide risk (King & Merchant, 2008).

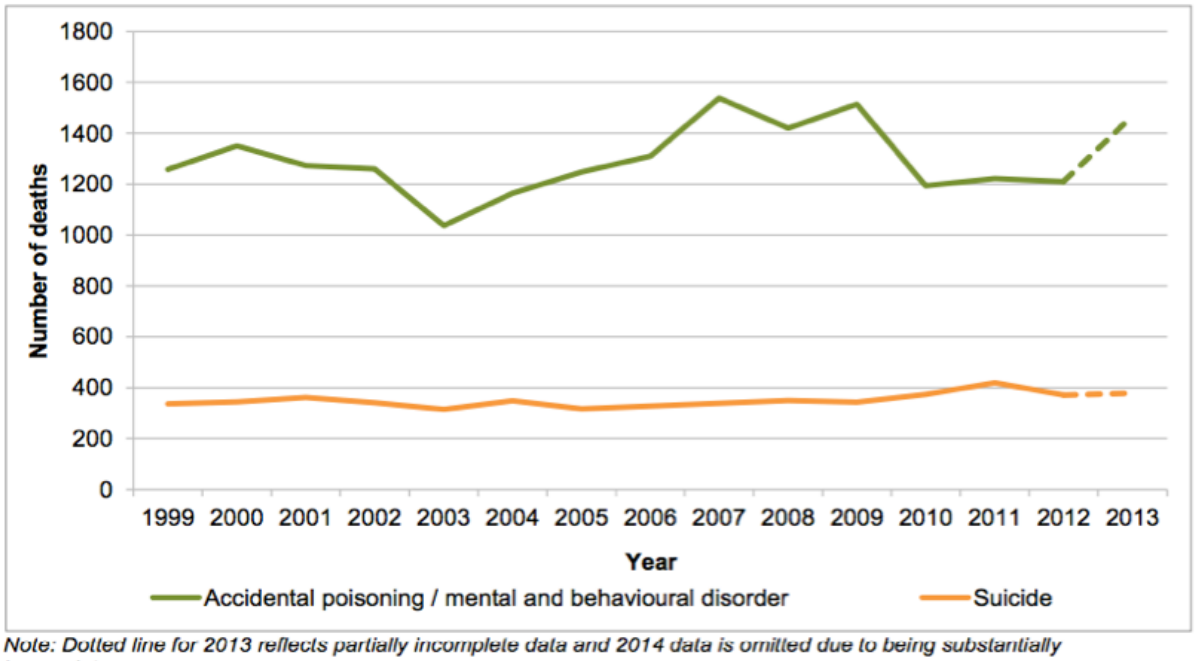
Research has consistently identified a considerable gender difference in suicide risk in OUD. Studies indicate that, while females are three times more likely than males to attempt suicide, males are three times more likely to complete suicide (Diekstra & Gulbinat 1993). Males predominantly employ violent methods for suicide, such as shooting and hanging, while females are more likely to employ non-violent methods such as drug poisoning (Tsirigotis et al., 2011). This gender difference in suicide method may at least partially explain the male predominance in completed suicides.

In the case of drug-poisonings, it is necessary to distinguish between suicide and accidental overdose. Differentiating deliberate and accidental heroin overdose can be problematic, due to ambiguous circumstantial information and unclear intent (Cantor et al., 2001).

Several authors have noted an overall association between heroin overdose and suicide (Best et al., 2000; Murphy et al., 1972; Neale 2000; Rossow & Lauritzen 1999) and suicidal intent is argued to occur in at least some of the of overdose cases (Best et al. 2000; Neale 2000). However, most studies have concluded that the majority of overdoses are accidental (Best et al., 2000; Darke et al., 2000; Darke & Ross 2001). The latest figures on drug related deaths in England and Wales also report that most opioid misuse deaths are accidental poisonings (PHE, 2016), the proportion of drug-misuse deaths which are suicides was 28% in females and 11% in males in 2015 (ONS, 2016). However, limitations in coding and methodology are also noted (ONS, 2014). Figure 1.2 below indicates that accidental overdose fatalities make up a larger proportion of drug related deaths than suicides in England and that this has been consistently the case over a number of years (PHE, 2016).

As will be explained in later chapters, where cause-specific mortality is analysed, the primary focus of this thesis is on overdose fatalities. Therefore, both deliberate drug poisonings (i.e. suicide) and unintentional drug poisonings (i.e. accidental overdose) are grouped together, but with violent suicides grouped into unnatural deaths. The assessment of suicide risk and subsequent detection of suicidality in OUD patients is explored in detail in Chapter 4.

Figure 1.2 Drug misuse deaths, by underlying cause of death by year of registration (PHE, 2016).



Note: Dotted line for 2013 reflects partially incomplete data and 2014 data is omitted due to being substantially incomplete

1.6.3 DISEASE

There are specific disease risks associated with illicit opioid use that occur at much lower levels amongst the general population. Hepatic, infectious, respiratory and circulatory diseases form a large proportion of deaths in opioid dependent patients (as will be explored in Chapter 3) (Darke et al., 2006; Pierce et al., 2015).

People who inject drugs (PWID) are at particular risk of infection with HIV or HCV transmitted through shared needles and syringes or through unprotected sexual activity (in the case of HIV) (Nelson et al., 2011; Page et al., 2013). Injecting drug use is thought to be the primary risk factor responsible for the spread of HIV in Eastern

Europe, Central Asia and Latin America (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2004). In England, Wales and Northern Ireland, 1.0% of the PWID surveyed in 2014 were infected. Among those attending needle and syringe programs in Scotland during 2013-14, 0.8% were HIV antibody positive (PHE, 2015a). In 2013 alone, 530 deaths among people with HIV in England and Wales were reported (PHE, 2015).

HCV is a disease of the liver which, if not resolved, can lead to chronic liver disease, cirrhosis and cancer. HCV is also a more robust virus than HIV and more easily spread (EMCDDA, 2016). The incidence of HCV among PWID in Europe is high (range 2.7–66 per 100 person-years, median 13), according to a recent review (Wiessing et al. 2014). Hahné et al. (2013) estimated the prevalence of anti-HCV (HCV positive test result) in PWID was on average almost 50 times higher than that in the general population. Co-infection of HIV and HCV is also common, with prevalence as high as 70-95% (Strader, 2005; Wiessing et al. 2014).

PHE estimates that 160,000 people in England are living with HCV. Between 2005 and 2014, deaths from HCV-related end-stage liver disease and hepatocellular carcinoma (liver cancer) in the UK more than doubled, rising from 215 in 2005 to 457 in 2014 (PHE, 2015).

Pulmonary diseases are also common in this patient group. PWID have a 10-fold increased risk of community-acquired pneumonia compared with the general population (Hind, 1990). The incidence of tuberculosis in those who misuse heroin increases by 6-fold compared to the general population, and 13-fold if the heroin user is also HIV positive (Story et al, 2007).

CHAPTER 2 MORTALITY RISK FACTORS IN OPIOID USERS: LITERATURE REVIEW AND THESIS RATIONALE

2.1 CHAPTER OVERVIEW

This chapter discusses key mortality risk factors in people who misuse opioids. These risks are categorized into patient-level risk factors and service-level risk factors. The former includes risks associated with socio-demographic factors, concomitant drug use and psychiatric well-being. The latter focuses on assessment of drug-related risks in secondary drug and alcohol services, risks associated with cessation of OST and those associated with disruptions in patient care (such as that during a transfer of patient and their care to an alternative service provider). Research limitations and gaps in existing literature are discussed, thereby providing a rationale for the current thesis.

2.2 MORTALITY RISK FACTORS: PATIENT-LEVEL

2.2.1 SOCIO-DEMOGRAPHIC FACTORS

Table 2.1., below, presents known demographic and psychosocial risk factors associated with increased mortality amongst opioid users, which will be described here and in the following subsections.

Although recent evidence (Pierce et al., 2015) shows a narrowing gender-specific risk with age, being male is still considered a risk factor for mortality, especially fatal overdose, amongst heroin users. The majority of deaths worldwide attributable to heroin use occur amongst males (Degenhardt et al., 2011). Males constitute around three-quarters of deaths in both cohort and coronial studies (Bargagli et al., 2001; Bartu et al., 2004; Cornish et al., 2010; Darke, 2011; Davoli et al., 1997; Davoli et al., 2007; Ghodse et al., 1998; Gossop et al., 2002; Pierce et al., 2015; Oppenheimer et al., 1994), and an overwhelming number of fatal overdoses, with some studies showing rates up to 80% (Darke et al., 2000; Davidson et al., 2003; Fugelstad et al., 2003; Hickman et al., 2003; Preti et al., 2002).

Given that most heroin users typically begin their heroin use in their late teens, age at first drug-use is also an important factor to consider because longer duration of heroin-using has been related to higher risk of mortality (Brugal et al., 2005). While death among young heroin users does occur, it is the older and more experienced user who is at most risk of death, as older age (older age relative to age at first use - i.e. 30 years old and over) is repeatedly reported as an independent predictor of mortality (Bargagli et al., 2001; Bartu et al., 2004; Cornish et al., 2010; Ghodse et al., 1998; Gossop et al., 2002; Pierce et al., 2015; Stebnacka et al., 2010).

The social profile of a typical heroin user is also one of poverty, which is known to increase mortality considerably (Coffin et al., 2007). Studies of street heroin users, those entering treatment and those in treatment almost universally report that most heroin users are unemployed, with rates ranging from two-thirds to 90% (Bell et al., 2007; Haasen et al., 2007; Hser et al., 1999; Maloney et al., 2009; Ross et al., 2005). Relating to this, the majority of heroin users have not completed high school and university qualifications are rare (Coffin et al., 2007; Darke et al., 2010b). Lower socio-economic status, including homelessness and housing instability, is common among mature users (Coffin et al., 2007) and is known to be associated with higher levels of psychopathology, poorer health and is a risk factor for overdose and mortality (Darke & Ross, 2001; Lee et al., 2013; Kerr et al., 2007).

Table 2.1 Key patient-level factors associated with increased overdose and mortality in opioid users.

Variable	Risk factor	Key studies
Gender	Males	Bargagli et al., 2001; Bartu et al., 2004; Davoli et al., 1997; Davoli et al., 2007; Ghodse et al., 1998; Gossop et al., 2002; Oppenheimer et al., 1994; Pierce et al., 2015
Age	Older opioid users (30y/o+)	Bargagli et al., 2001; Bartu et al., 2004; Cornish et al., 2010; Ghodse et al., 1998; Gossop et al., 2002; Pierce et al., 2015; Stebnacka et al., 2010
Socio-economic status	Low	Amundsen, 2015; Darke & Ross, 2001; Davoli et al., 1993; Hser et al., 2001; Lee et al., 2013.
Treatment status	Not enrolled	Darke et al., 2000; Davidson et al., 2003; McGregor et al., 1998; Pierce et al., 2016
Tolerance	Reduced	Cornish et al., 2010; Cousins et al., 2015; Davoli et al., 2007; Merrall et al., 2010; Ravandal & Amundsen, 2010; Singleton et al., 2003; Strang et al., 2003; Tagliaro et al., 1998
Polydrug use	Alcohol and other CNS depressants	Darke et al., 2010; Davidson et al., 2003; Degenhardt & Hall, 2012; Fugelstad et al., 2003; Hickman et al., 2003; Kerr et al., 2007; Pierce et al., 2016; Preti et al., 2002
Psychiatric wellbeing	Poor. High levels of psychopathology	Arendt et al., 2011; Bargagli et al., 2006; Darke & Ross 2002; Ghodse et al., 1985; Gossop et al., 2002; Davoli et al., 1993; Shah et al., 2008
Route of opioid administration	Injecting	Brugal et al., 2002; Carpenter et al., 1998; Darke et al., 2005b; Milloy et al., 2008; Pierce et al., 2016; Swift et al., 1999; Yin et al., 2007;

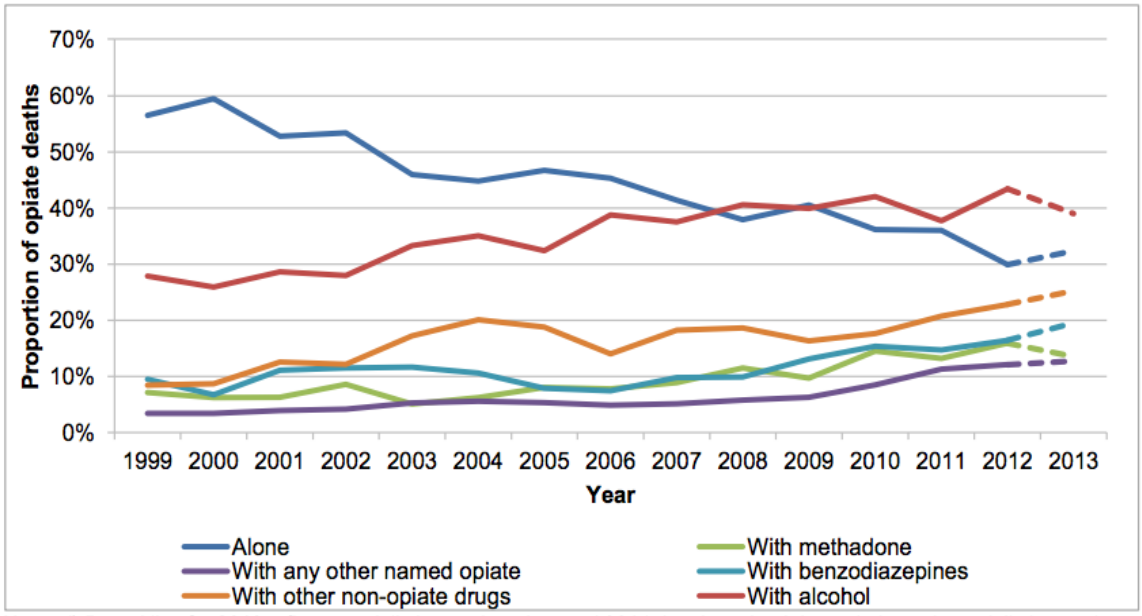
2.2.2 CONCOMITANT DRUG USE

Possibly the most important finding to emerge from heroin overdose research is the role of polydrug use (Darke, 2011). The overwhelming majority of overdoses, both fatal and non-fatal (Darke et al., 2010; Davidson et al., 2003; Degenhardt & Hall, 2012; Fugelstad et al., 2003; Hickman et al., 2003; Pierce et al., 2016; Preti et al., 2002) involve the concomitant consumption of heroin with other drugs. The extent of polydrug use among "heroin" overdoses suggests that "polydrug toxicity" is a better description of the toxicology of overdose (Darke & Zador, 1996). The major drugs associated with an increased risk of fatal and nonfatal heroin overdose are alcohol and benzodiazepines (Warner-Smith et al., 2001).

Alcohol is, by far, the most common concomitant drug and is present in a half or more of fatal overdose cases (Darke & Zador, 1996; PHE, 2016; Sporer, 1999; Warner-Smith et al., 2001). Figure 2.1 displays a general falling trend in the proportion of heroin deaths where only heroin was mentioned (30% in 2012), whereas the proportion where alcohol was mentioned alongside heroin has increased and now exceeds the figure for heroin alone (being 43% in 2012) (PHE, 2016).

Studies report rates of current drinking by heroin users as ranging between 25-75% and with about a quarter or more drinking to excess daily (Darke et al., 2006, Quan et al., 2007). Consistent with this view, high levels of alcohol dependence among OUD patients is present (as will be explored in Chapter 4). Studies report the presence of AUD ranging between 25% to 50% amongst OUD patients (Cacciola et al., 2001; Darke & Ross et al., 1997a; Hser et al., 1999; Maloney et al., 2009).

Figure 2.1 Heroin deaths by other substances mentioned alongside heroin, by year (PHE, 2016).



Notes: i) Dotted line for 2013 reflects partially incomplete data and 2014 data is omitted due to being substantially incomplete (see reporting methodology) ii) An individual death may be counted under more than one category, except 'Alone' which is exclusive from other categories

An extensive literature focus on the link between overdose deaths and the concomitant use of alcohol and heroin (Darke et al., 2010; Davidson et al., 2003; Fugelstad et al., 2003; Hickman et al., 2003; Preti et al., 2002). While the co-use of alcohol and heroin poses a serious risk of fatal overdose, relatively limited attention has been given to investigations beyond overdose deaths (Johnson et al., 2015).

Independently of opioid use, heavy alcohol use and dependence is associated with a higher risk of mortality (Harris & Barrclough, 1998), including liver disease, cardiovascular disease, cancers, suicide and traumatic accidents (Murray et al., 1997). Liver disease is particularly problematic in the heroin using population due to high rates of HCV. Therefore, any additional use of alcohol in conjunction with hepatic

disease might speed up the progression of liver disease. The risk of developing cirrhosis in patients who are HCV-positive and abuse alcohol is 147 times greater than HCV-positive patients who abstain (Poynard et al., 1997).

Although previous studies have denoted that fatal overdose accounts for the majority of deaths in the illicit drug using population (Darke & Hall, 2003; Brugal et al., 2005), other acute and chronic diseases also contribute to mortality. This is especially true for PWID, where the majority of non-overdose related deaths are attributable to preventable risk factors including infectious disease and suicide (Johnson et al., 2015; Miller et al., 2007). This limitation was raised in a recent publication (Johnson et al., 2015) but specific non-overdose causes were not fully explored (a limitation which is addressed in Chapter 4). Furthermore, there also seems to be contradictory evidence with regards to overdose - that although a major cause, overdose accounted for a minority of premature mortality in a recent, large, English cohort (Pierce et al, 2015). There may also be epoch effects /geographical variability (vs. non-UK) due to the ageing – thus increased vulnerability to disease/overdose due to accelerated ageing - of UK opioid user cohorts that initiated use in the 1980s/90s.

2.2.3 PSYCHOLOGICAL WELL-BEING

OUD is also strongly associated with other psychiatric disorders, especially mood and personality disorders, in both clinical (Brooner et al., 1997; Weaver et al., 2003) and general population samples (Rodriguez-Llera et al., 2006). Lifetime psychiatric comorbidity ranges from 44% to 93% amongst the heroin using population (Brooner et al., 1997; Cacciola et al., 2001; Khantzian and Treece, 1985; King et al., 2000; Krausz et al., 1999; Mason et al., 1998).

Individuals with OUD are at risk of developing mild to moderate depression that meets symptomatic and duration criteria for persistent depressive disorder (dysthymia) or, in some cases, for major depressive disorder (Compton et al. 2005). These symptoms may represent an opioid-induced depressive disorder or an exacerbation of a pre-existing primary depressive disorder. Periods of depression are especially common during chronic intoxication or in association with physical or psychosocial stressors that are related to the opioid use disorder (APA, 2013).

Antisocial personality disorder is a rare diagnosis in the general community (4%) (Robins and Regier, 1991), but has been reported to occur at rates of up to 65% in heroin-using samples (Bargagli et al., 2006; Compton et al., 2005; Darke et al., 1994). In addition, people with a diagnosis of PD have a four-fold higher mortality, with substantially reduced life expectancy (Fok et al., 2012). Similarly, substantially higher mortality rates are found in people with SMI and depressive disorders when compared to the general population (Chang et al., 2010).

Psychiatric comorbidity is associated with poor treatment prognosis, greater psychosocial impairment, increased risk of relapse and higher rates of HIV risk behaviour (Arendt et al., 2007; Brooner et al., 1997; Darke and Ross, 1997; Disney et al., 2006; Landheim et al., 2006; Rounsaville et al., 1982, 1998). In spite of this, the impact of psychiatric comorbidity on mortality risk in substance use disorders has received only moderate attention, with existing investigations reporting mixed results (Arendt et al., 2011; Gossop et al., 2002; Mattisson et al., 2011)

For example, a nationwide Norwegian study found no associations between psychiatric comorbidity (schizophrenia-spectrum disorder, affective disorder, personality disorder) and all-cause mortality in heroin/opioid users (Arendt et al., 2011). Gossop and colleagues (2002) on the other hand, presented findings of the association between psychological problems and mortality, but the results were somewhat unexpected because higher levels of anxiety were predictive of increased mortality but no statistically significant association was found between depression and mortality. This study, as well as others (Bartu et al., 2004; Johnson et al., 2005; Ravndal & Vaglum, 1998), also only assess one type of symptom (e.g. anxiety score, thoughts of suicide) rather than psychiatric diagnosis; and are limited to investigations of only all-cause or drug-related deaths and often does not specifically investigate natural causes of death (as discussed earlier). Results presented in Chapter 4 explore psychiatric comorbidity in OUD patients in more detail.

2.3 MORTALITY RISK FACTORS: SERVICE-LEVEL

2.3.1 ASSESSMENT OF RISK

Assessing and managing risks is a paramount element of care planning and treatment provision for people with drug dependence, particularly in opioid dependence where risk of mortality is especially high (DoH, 2007). Structured risk assessments are frequently used but the NTA advises that risk assessments should be substance misuse specific, prioritizing risks directly related to opioid dependence (NTA, 2006a; 2006b)

However, the effectiveness of risk assessment tools in predicting mortality in mental healthcare is still unclear. Wand and colleagues reported the inability to conduct a systematic review due to paucity of studies evaluating the effectiveness of risk assessments and found little evidence to conclude whether risk assessments are effective in relation to self-harm or suicide reduction (Wand, 2012). Other studies attempting to identify high-risk individuals have been largely unsuccessful primarily due to its low prevalence, even within high-risk groups (Harris & Hawton, 2005)*;* or were limited to all-cause mortality and generalized mental-health diagnosis (Wu et al., 2012).

Within South London and Maudsley (SLaM) NHS Foundation Trust, substance misuse and dependence relevant risks are recorded using the Brief Risk Scale Assessment for Addictions (BRSA-A) (see Chapter 5) – a measure developed by SLaM addiction clinicians to encourage identification and formal recording of risk areas specific to substance misuse patients; and used in their care planning (SLaM, 2011). However, no formal evaluation of this risk tool was conducted and Chapter 5 addresses this gap.

2.3.2 "SUCCESSFUL" END OF TREATMENT

OST is the most widely used treatment approach for opioid dependence and it is associated with substantial reduction of heroin use and associated risks (Brugal et al., 2005). Overdoses overwhelmingly occur when the person is not enrolled in drug treatment (Darke et al., 2000; Darke et al., 2005; Davidson et al., 2003). An important feature to be noted (and one which this thesis considers) is that the picture here is of high heroin tolerance due to frequent use. However, there are occasions of reduced tolerance that increase transient overdose risk (Cornish et al., 2010; Cousins et al., 2016; Davoli et al., 2007; Merrall et al., 2010; Ravndal & Amundsen, 2010; Singleton et al., 2003; Strang et al., 2003; Tagliaro et al., 1998).

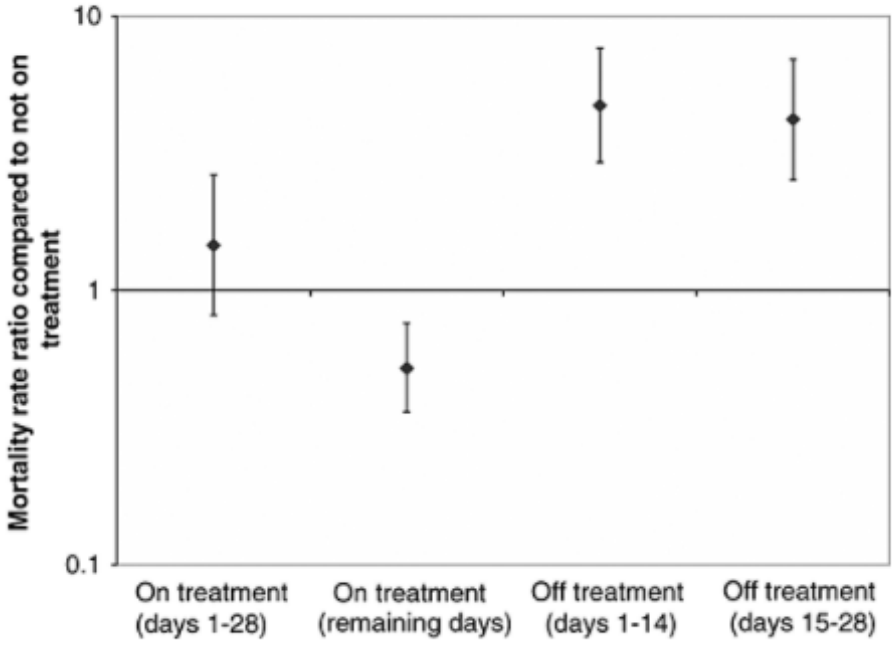
There appears to be a transient elevated risk of death in the very early stages of treatment (first 28 days) (Degenhardt et al., 2009) and following the end of OST treatment (Cornish et al., 2010; Davoli et al., 2007; Cousins et al., 2016).

Table 2.2. summarises results and limitations of studies which have specifically investigated mortality after discharge from services in opioid users. The search strategy for this peer-reviewed study search was conducted in PubMed/MEDLINE and PsychINFO, using Boolean operators for opioid / heroin / opiates / drug-use / substance (ab/mis)use and death / mortality and treatment / discharge / detoxification (wildcards were used where appropriate). The search was restricted to originally published research between 1980 – 2016. Hand search through references of relevant studies was also conducted, which is how two meta-analysis (Degenhardt et al., 2010; Mathers et al., 2013, included in Table 2.2) were found.

To summarize, Strang and colleagues (2003) conducted a small study to test whether loss of tolerance increased the risk of overdose and found that patients who "successfully" completed inpatient detoxification ("lost tolerance" group) were more likely than other patients to have died within a year. None of the patients who failed to complete detoxification (i.e. dropped out) died.

These findings were subsequently confirmed by larger studies (Cornish et al., 2010; Cousins et al., 2015; Davoli et al., 2007; Merrall et al., 2013). A large Italian study (Davoli et al.,2007) demonstrated higher excess mortality by overdose in the first 30 days after treatment completion or cessation: more than three times higher than subsequent period 31 or more days after treatment. Cornish (2010) found that the risk of death increased eightfold to ninefold in the month immediately after the end of OST (presented in Figure 2.2 below). They also found no strong evidence that these effects varied according to the type of treatment (methadone or buprenorphine) or whether cessation of treatment had been planned or unplanned.

Figure 2.2 Adjusted risk of death, compared with not being on treatment, during and after opiate substitution treatment (Cornish et al., 2010).



However, as presented in Table 2.2 below, several limitations in literature investigating mortality rates after cessation of treatment were noted. First, studies are limited to very small or inpatient or methadone or primary healthcare only samples (Cornish et al., 2010; Cousins et al., 2016; Strang et al., 2003; Rvandal & Amundsen, 2010; Merrall et al., 2013), therefore limiting generalizability of findings to specific OUD subgroups. Problems with residual confounding is also likely as associations between treatment exit and mortality often included crude measures (Clausen et al., 2008; Dagenhardt et al., 2009; Fugelstad, 1995; Mathers et al., 2013; Strang et al., 2003) or limited adjustment for potential confounders (Bjornaas et al., 2009; Davoli et

al., 2007; Merrall et al., 2013). Davoli et al., (2007) for example did not adjust for any socio-demographic factors other than age and gender.

Second, while a study carried out by Cornish et al., (2010) is the most comprehensive one to date, it is inclusive of only primary health care OUD patients, thereby not including a large proportion of patients receiving care through secondary services, who are likely to have more severe levels of dependence. Also, specific causes of death were not explored. This study, however, was the only study to have compared planned and unplanned cessations of OST treatment. Although no difference was found between the two exit types, the planned discharge was based on tapering down of OST medication dose rather than a direct indication of discharge.

Inconsistencies around misclassification of patients into on or off treatment episodes were also present. Some studies have considered that a gap of less than 28 days between the end of one on treatment episode and the start of the next one is not long enough to assume that a patient would genuinely stop and restart treatment within a 4-week period (Cornish et al., 2010). Other studies, however, have categorized patients into an off treatment group after just the 3rd consecutive day of missed OST dose (Cousins et al., 2015; 2011), or after the 7th missed dose (Degenhardt et al., 2009).

Moreover, a recently published commentary by Hickman and colleagues (2016) stressed that further evidence on risk of mortality on and off OST is needed. The commentary summarises that more studies of this kind are necessary so that 'stratified medicine' for treatment of OUD can be provided. Pooled experience and evidence from different health-care systems is necessary in order to tailor specific treatments

and ensure that ‘the right patient gets the right treatment at the right time’. Chapters 6 and 7 explore mortality post cessation of OST in more detail.

Table 2.2 Studies investigating mortality after discharge from services in opioid users.

Author	Location	Study sample	Results	Limitations of relevance
Bjornaas et al., 2009	Oslo, Norway	N=110 opioid 'addicts'; n=47 all-cause deaths among opioid users.	Opioid addiction was associated with a twofold increase of all-cause mortality during a 20-year follow-up after discharge from general hospital following self-poisoning (compared to the general population on Norway). OUD did not predict further suicide.	Very limited adjustment for potential confounders; classification of opioid addiction based on patient interviews at the time of admission with no further follow-up; no information regarding substance related treatment pre – or post-self-poisoning
Cornish et al., 2010	UK	N=5577 OST patients; n=178 all-cause deaths	All-cause mortality in the first month after cessation of OST treatment was more than 8 times higher, compared with 28+ days of OST maintenance.	Primary healthcare cohort; no specific causes of deaths reported; patients transferred out of services were considered lost to follow-up; limited adjustment for potential confounding; planned cessation of treatment based on tapering down of dose rather than a direct indication of discharge.

Author	Location	Study sample	Results	Limitations of relevance
Clausen et al., 2008	Norway	N=3,789 OUD patients; n=77 deaths (n=61 OD)	Patients post-treatment had reduced all-cause and OD mortality rate compared to that pre-treatment (rate ratio [RR]=1.4). Mortality in treatment was reduced, compared to that pre-treatment, in both all-cause and OD mortality (RR=0.50; RR=0.20)	Crude estimations; no information of the type of maintenance treatment, drug use history, or whether exit from treatment was planned or not. No information with regards to disruptions in treatment. Inclusion to OST treatment in Norway varies to that in the UK in terms of severity of dependence required to enter, so results may not be generalizable to the UK.
Cousins et al., 2016	Ireland	N=6,983 patients prescribed methadone; n=213 deaths; n=78 DRD (drug related deaths)	Overall, all-cause mortality off-treatment was more than 3 fold higher than that on treatment. All-cause mortality off-treatment was over 6 times higher in the first 2 weeks and 9 times higher in weeks 2-4, compared with time 5+ weeks on treatment. However, adjusted DR mortality overall and in	Methadone-prescribed patients only; primary care cohort; limited adjustment in the DRD models; transfer of patients and other disruptions in treatment not reported; mixed findings with regards to DRD; cessation of methadone treatment established after 3rd consecutive day of missed dose; planned vs unplanned

Author	Location	Study sample	Results	Limitations of relevance
			period specific analysis was not significant.	cessations of treatment not investigated.
Cousins et al., 2011	Ireland	N=2,048 patients prescribed methadone; n=64 DRD	Risk of DRD was minimally lower after the first 30 days following cessation of methadone treatment, relative to the first 30 days off treatment.	Methadone prescribed primary care cohort; planned and unplanned treatment cessations not investigated. Cessation of treatment established after 3rd consecutive missed methadone. Transfers and other disruptions in treatment not reported. Mixed, possibly underpowered results owing to limited number of deaths.
Dagenhardt et al., 2009	Australia	N=42,676 in OST treatment; n=3,803 deaths; n=87 DRD	Excess mortality in first 2 weeks after cessation of treatment compared to the general population. Also high risk of mortality in first two weeks after starting treatment was also found.	Crude estimations; planned and unplanned exits from treatment not explored. New treatment episode defined at 7+ days after the end of the previous episode.

Author	Location	Study sample	Results	Limitations of relevance
Degenhardt et al., 2010	N/A	N=2832 all-cause deaths across 6 studies; n=1427 OD deaths across 6 studies	CMR were 2.38 times higher for time spent out of treatment compared to in-treatment periods. OD was 3.5 times higher compared to time in treatment – Meta-analysis of 6 studies.	Crude estimations. Transfer periods not taken into account.
Davoli et al., 2007	Italy	N=10,454 heroin users in treatment; n=41 OD.	The risk of fatal OD for patients out of treatment was 11 times higher than that in treatment, after adjustment. Adjusted OD hazard ratio (HR) within 30 days of cessation of treatment was 26.6.	Low number of OD deaths in groups. Cohort was not restricted OST and included psychosocial and therapeutic community interventions where overall out of treatment risks appeared to be highest. Limited socio-demographic adjustment. Transfers and disruptions of care not reported. The follow-up time for patients out of treatment was substantially lower than that on treatment and examination of differences in risk between treatment modalities was limited.

Author	Location	Study sample	Results	Limitations of relevance
Fugelstad, 1995	Sweden	N=135 HIV+ PWID in methadone programme; n=69 deaths (n=52 deaths due to violence or poisoning).	RR ratio for mortality attributed to violence or poisoning for patients discharged from methadone treatment was 2.9 times higher compared to those never admitted, within a 4-year follow-up	Crude estimations. Cohort inclusive of HIV+ PWID in residential treatment only. Specific risk periods not explored; Planned treatment cessations and drop-outs not reported.
Fugelstad, 1998	Sweden	N=101 OUDs in residential treatment; n=40 deaths	N=24 / 29 people died from non HIV related causes in the 3-year follow-up after cessation of treatment.	Inclusive of patients in OST and non-OST, residential treatment; 55% patients HIV+
Mathers et al., 2013	International	Meta-analysis of 6 cohort studies in PWID	Meta-analysis suggested crude all-cause mortality was 2.5 times higher during off-treatment periods than in treatment periods.	Crude estimations of 6 studies, described within this table separately. Cohort inclusive of PWID only.
Merrall et al., 2013	Scotland	N=69,457 drug users; n=45,378 opioid users; n=1383 DRD	DRD rate within 28 days after inpatient discharge (any kind of hospitalisation) was 21 times higher, for drug users registered with addiction services	Comparisons of periods on and off treatment are inclusive of drug users in cohort (not separated by substance use problem); includes instances where

Author	Location	Study sample	Results	Limitations of relevance
			Referent group were drug users never admitted for hospitalisation.	unsuccessful resuscitation attempts were made on site, therefore introducing potential misclassification of a "hospital episode". Limited adjustment for potential confounding.
Ravndal & Amundsen, 2010	Norway	N=276 inpatient drug users; n=36 deaths (n=24 OD)	Unadjusted elevated risk of OD within 4 weeks of leaving medication-free inpatient treatment was 29.9.	Inpatients drug users, unknown number of opioid users. Limited adjustment for potential confounders. End of treatment included voluntary drop-outs and planned completion with the view to continue psychosocial rehabilitation elsewhere (which constitutes a transfer to another therapy), which were not investigated seperately.
Strang et al., 2003	UK	N=137 inpatient OUD patients; n=5 deaths	Total of 5 patients died within 12 months post-discharge from inpatient opiate detoxification programme. Three	Descriptive analysis. Small sample inpatient OUD patients. Low number of deaths.

Author	Location	Study sample	Results	Limitations of relevance
			died of OD within first 4 months. All 3 OD deaths occurred in patients who "successfully" completed detoxification.	
White et al., 2015	Scotland	N=98,000 drug users; n=1409 DRD	DRD rate within 28 days after discharge from general hospital was 15 times higher. Referent group were drug users never admitted into services.	Inclusive of inpatient general hospital admissions; insufficient power to fully investigate the effect of longer hospital stays (where a loss of tolerance would occur). Comparisons of post-discharge to those who were never admitted inclusive of all drug-users without providing estimates for those with OUD.

2.3.3 DISRUPTIONS IN PATIENT CARE

Interruptions of continuity of care is a current area of concern. The Advisory Council on the Misuse of Drugs (ACMD, 2015) has recently highlighted that frequent re-procurement of local drug treatment services (every 3 to 5 years) and cuts in resources, which often result in group-transfer of patients to alternative service providers, could have a negative impact on treatment outcomes. At present, however, very little is known with regard to de-stabilisation that may occur with changes to service delivery. Evidence from a survey of commissioners and surveys of providers (DrugScope, 2015) indicates that frequency of re-procurement appears to have a de-stabilizing and negative impact on local service user recovery outcomes.

No studies have investigated the possible impact of disruptions in OUD patient care, treatment outcomes and mortality. Although the studies presented in Table 2.2 have examined risks associated with planned and unplanned cessations of OST treatments, none has taken into account disruptions in patient care (other than patient drop out), such as a transfer of patient and their care into an alternative service provider during their OST (a limitation which is addressed in Chapters 6 and 7).

The study carried out by Cornish and colleagues (2010) does report that approximately 10% of patients per annum were transferred out of services in their cohort, but these patients were considered lost to follow-up and not investigated further. A larger proportion of transferred patients might be expected in secondary care, as these would include a “step-down” transfer from secondary to primary healthcare, as well as those transferred after re-organizational changes. Ravndal &

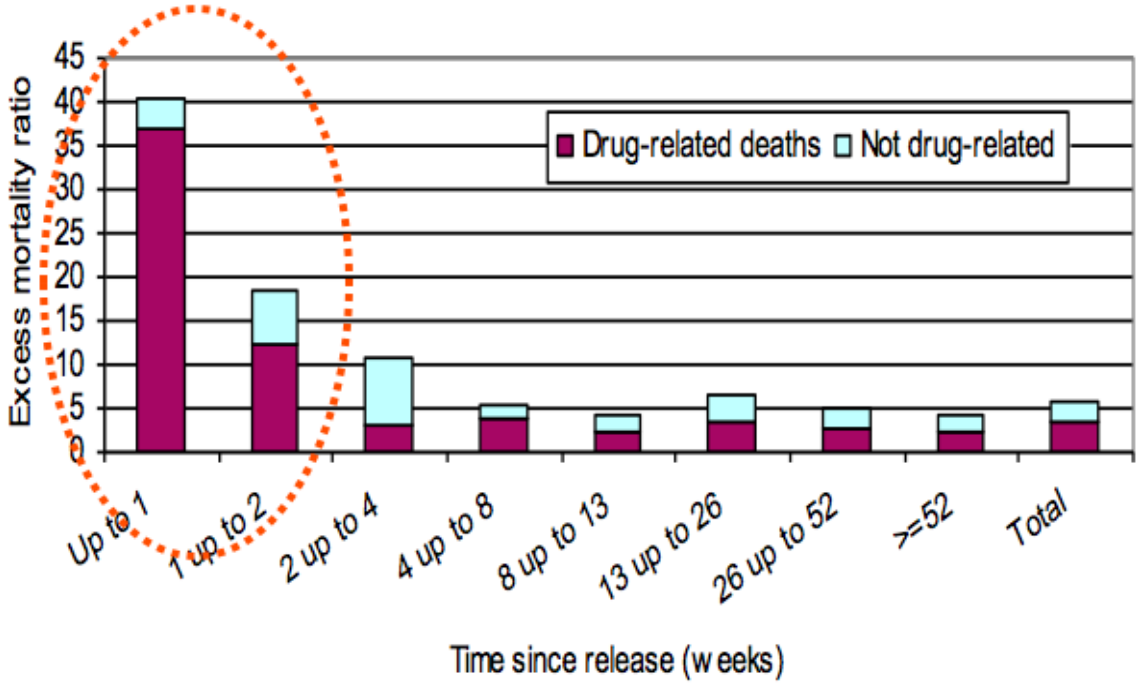
Amundsen (2010) defined “discharge” from treatment as completion of inpatient treatment and a transfer to psychosocial rehabilitation. The study reported unadjusted excess overdose mortality rate ratio of 15.7 but all deaths occurred in patients who had dropped out of treatment and inpatient treatment did not involve prescription of any OST.

Similar limitations are seen in post-prison release studies. It is recognized both in the United Kingdom (Bird & Hutchinson, 2003; Farrell & Marsden, 2008; Seaman et al., 1998) and internationally (Merrall et al., 2010) that recently released prisoners, notably those with a history of having injected heroin, are at very high risk of DRD.

This increased risk is concentrated in the first 2 weeks after release from prison. For example, Seaman et al. (1998) reported that male HIV-infected drug injectors had a RR of DRD of 8 during the first 2 weeks after release versus other comparable times at liberty. Bird & Hutchinson (2003) found that males had a DRD risk seven times higher in the first 2 weeks compared to the subsequent 10 weeks. Further, 60% of DRD within 12 weeks of release had occurred within the first 2 weeks.

These findings have since been confirmed in record-linkage studies in England and Wales (Farrell & Marsden, 2008), Australia (Kariminia et al., 2007) and the United States (Merrall et al., 2010). A larger scale study in England and Wales confirmed the extraordinary concentration of excess mortality post-release as occurring particularly during the first fortnight post-release (presented in Figure 2.3. below).

Figure 2.3 Excess mortality ratio for different time periods post-release by cause of death (Singleton, 2003).



Provision of OST in prisons, besides being good clinical practice, has contributed to a reduction of in-prison deaths (Bird, 2008; Larney et al., 2014) and of injecting while in prison (including blood-borne virus transmissions) (Stallwitz & Stöver, 2007; Taylor et al., 2013). Another possible benefit of prison-based OST might be to prevent the loss of opiate tolerance, thereby reduce the risk of DRD after release – that is, during the transfer period between prison and post-release drug and alcohol service provision.

Unfortunately, literature on the transfer of patient care and provision of OST medication pre- and post-release through transitional care programs remains inconclusive (Merrall et al., 2010; Farrell & Marsden, 2008). Only four studies (Bird et

al., 2015; Degenhardt et al., 2014; Kariminia et al., 2007; Merrall et al., 2010) have monitored the impact of prison-based OST on DRD risk soon after prison release.

In Australia, Degenhardt and colleagues (2014a) reported that the proportion of 12-week post-treatment DRD that occurred in the first 2 weeks was approximately 50% in 2000–10, unchanged from 1988 to 2002 (Kariminia et al., 2007; Merrall et al., 2010), although prison-based OST had been received in 58% of opiate-dependent clients' prison episodes.

Following the introduction of a prison-based OST policy in Scotland, the rate of drug-related deaths in the 12 weeks following release fell by two-fifths. However, the proportion of deaths that occurred in the first 14 days did not change appreciably, suggesting that in-prison OST does not reduce early deaths after release (Bird et al., 2015).

A large-scale, observational study of 20,000 heroin-addicted prisoners assigned to opioid maintenance treatment (or to abstinence) is currently being conducted in England and Wales. Findings from this investigation will shed light on the benefit obtained and on ways to improve prison health care and, crucially, on continuity of care on release from prison and return to the community (Strang, 2015). Similar investigations are also necessary to investigate transfers of patients between drug and alcohol services, where OST is arranged to continue (Chapters 6-7).

2.4 SIGNPOSTS TO THE SCOPE OF COVERAGE IN SUBSEQUENT CHAPTERS

Chapter 4

Given the high prevalence of comorbid alcohol, mood problems, PD and SMI among opioid users and particularly high hazard ratios for mortality risk in individuals with these diagnoses (as explored earlier in this chapter), it is plausible that these psychiatric problems may contribute to the elevated mortality risk observed in this patient group, with regard to both natural and unnatural causes of death. Therefore, Chapter 4 investigates the impact of comorbid psychiatric problems in opioid users and looks beyond overdose mortality.

Chapter 5

Effective assessment of risk in OUD patients is paramount (DoH, 2007; NTA 2006a, 2006b). Risk assessments tools are widely used, but their ability to predict outcomes in OUD treatment remains unclear. The aim of Chapter 5 is to investigate if addiction-specific brief risk screening is effective in identifying high mortality risk groups and if subsequent clinical actions following risk assessment impacts on all-cause and overdose mortality levels.

Chapter 6

Overdose high-risk periods were identified immediately after release from prison, at the beginning of OST treatment and immediately post-detoxification with cessation of OST treatment. However, as noted in the literature review, existing research is limited and does not take into account disruptions in patient care (beyond drop-outs), such as transfers between services. Chapter 6 conducts an investigation of excess overdose mortality

immediately after cessation of opioid substitute therapy and following transfer of patients and their care, in opioid dependent individuals in specialist addiction treatment.

Chapter 7

Chapter 6 provided groundwork for much needed further research, requiring deeper exploration of findings. However, the preceding chapter was limited to crude estimations of clustering of deaths surrounding treatment cessations and transfers. In Chapter 7, I use an extended dataset and adjust for a broad range of confounders to explore mortality risks after a planned end of OST and post-transfer of patient and their care where OST was arranged to continue.

CHAPTER 3 DATA SOURCE AND DATA EXTRACTION METHODS

3.1 SUMMARY

The data used to conduct this PhD project were derived using the SLaM Biomedical Research Centre Clinical Record Interactive Search (CRIS) tool, developed for use within the NIHR Mental Health Biomedical Research Centre and Dementia Unit. The CRIS system, including mortality tracing at a national level, enables researchers to search and retrieve electronic patient health records in a de-identified format, with more than 280,000 cases currently represented on the system. In depth understanding of CRIS was essential to fully explore and appreciate the scope of my data. Therefore, this chapter describes the study setting and the operational models of the CRIS system. Key variables such as diagnoses, the scope of electronic patient records and all-cause and cause-specific mortality derived from linked data are also explained. In addition, automated extraction and coding of data from free text using Natural Language Processing (NLP) is described. Finally, a detailed account of limitations specific to CRIS and the approaches employed for data extraction are discussed.

3.2 SETTING

3.2.1 SOUTH LONDON AND MAUDSLEY NHS FOUNDATION TRUST

SLaM is one of the largest specialist mental healthcare services in Europe, which provides comprehensive mental healthcare and addiction services to a catchment population of approximately 1.2 million residents across seven multicultural, ethnically diverse, highly dense boroughs of London. SLaM provides the widest range of NHS mental health services in the UK, with services including the Maudsley Hospital and Bethlem Royal Hospital. SLaM works closely with the Institute of Psychiatry, Psychology and Neuroscience where this PhD was carried out; and are part of King's Health Partners Academic Health Sciences Centre. Within the framework of the NHS in the United Kingdom, mental health trusts have close to 100% monopoly for service provision to their geographic catchments.

3.2.2 ADDICTIONS SERVICES

Addictions services in SLaM are one of the largest providers of NHS addictions services in the UK, providing drug, alcohol and smoking cessation services. Addiction services are provided in the community through GP surgeries, outpatient services, specialist support clinics and inpatient services for people who require more in depth treatment and care. SLaM Addictions also provide specialist services for adults from around the country who need specialist care and treatment. The National Addiction Centre, part of King's College London, is within their portfolio of services and represents a network of clinicians, researchers and clinical teachers with a shared commitment in addiction research, prevention and treatment work, providing an excellent platform for clinical research.

3.3 CLINICAL RECORDS INTERACTIVE SEARCH

3.3.1 THE ELECTRONIC PATIENT JOURNEY SYSTEM

The SLAM electronic Patient Journey System (ePJS) is a bespoke, single, integrated electronic clinical records system used across all Trust services. It was designed primarily to support the recording and sharing of clinical information, whilst producing relevant management and national reports as a natural by-product. EPJS was implemented in most SLaM services in 2006 and in Addictions services in April 2008, replacing a number of independent clinical and administrative information systems used in the Trust at the time. All patient-based information for patients seen from 1999 onwards was migrated into ePJS from electronic legacy systems.

EPJS is a comprehensive record of all clinical information recorded throughout patients' journeys through Trust services, including demographic and contact information, dates and other details of referrals and transfers, detailed clinical assessments, care plans and medication, clinical activity and reviews. Imaging and laboratory data are not, to date, recorded there. The record is used and maintained by multi-disciplinary professionals and consists of both structured data (such as dates, integers and pick-lists) and unstructured free-text (including written assessments, progress notes, event notes and correspondence). EPJS includes specific assessments such as structured physical health assessments, cognitive function and outcome measures (such as the Health of the Nation Outcome Scale [HONOS], Treatment Outcome Profile [TOP] (see appendix vi.) and National Drug Treatment Monitoring System [NDTMS]).

3.3.2 THE CRIS SYSTEM

Rapid technological advantages and other developments over the last decade have led to new possibilities for case register development. In 2008, using electronic health records (EHRs) derived from ePJS, the CRIS system was developed for use within the NIHR Mental Health Biomedical Research Centre and Dementia Unit; and approved as a dataset for secondary analysis by Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5).

CRIS enables researchers, such as myself, to search and retrieve ePJS-based EHRs in a de-identified form. All data for this Ph.D. project were extracted using the CRIS tool. As a CRIS user, I was able to search for any combinations of structured and unstructured fields from ePJS health records (providing that these fields were within the scope of the research project, which had been approved by an oversight committee, described below), except that CRIS 'produced' these health records in a de-anonymised form. The development of CRIS required a strict security model with attention to legal and ethical considerations regarding the use of confidential health data, described in detail by Stewart and colleagues (Perera et al., 2015; Stewart et al., 2009).

Briefly, all CRIS users must firstly obtain a Letter of Access from the Research and Development Team, as well as project-specific approval from the CRIS oversight committee for each investigation. The oversight committee was formed not only to review all applications to use CRIS, but also to provide practical advice to researchers on how best to navigate and manipulate the complex and extensive data from more than 280,000 cases represented on the system. The SLaM BRC Clinical Record continues to grow as a database, with approximately 20,000 new cases added each year, in addition to extension of follow-up for existing cases.

3.3.3 FRONT-END CRIS

CRIS has two distinct search features. First, described here, is the 'front-end CRIS', which searches and retrieves information from the structured electronic health record fields - these may include information such as dates, numerical fields or drop-down menus; and from unstructured fields – these are user-defined text strings from ePJS records. For example, information submitted to the NDTMS, which collects, collates and analyses information from all drug treatment agencies, is recorded in the structured fields in ePJS and subsequently in CRIS. Structured forms, such as the BRSA-A (described further in Chapter 4), are also present in a structured and binary format and can be viewed or extracted using the front-end CRIS. The CRIS tool 'hits' relevant records based on search terms, such as 'opioid use disorder' diagnosis and/or a text string (e.g. "needle-exchange"). The results are then returned in spreadsheet format and are exportable as a CSV file for analysis.

An example, adapted from Stewart and colleagues (2009), of the front-end CRIS results table is represented in Figure 3.1 (due to data protection and confidentiality agreements, I could not present an example of front-end CRIS search table relevant to this PhD). Any combinations that match entries in structured name, date of birth and address fields in ePJS are replaced with 'ZZZZZ' in the searchable index. In addition, an anonymised Biomedical Research Centre (BRC) identifier is constructed from the patient's NHS number, which is then excluded from the searchable index. The algorithm for creating BRC identifiers from NHS number is hidden and cannot be accessed by myself and other front line researchers.

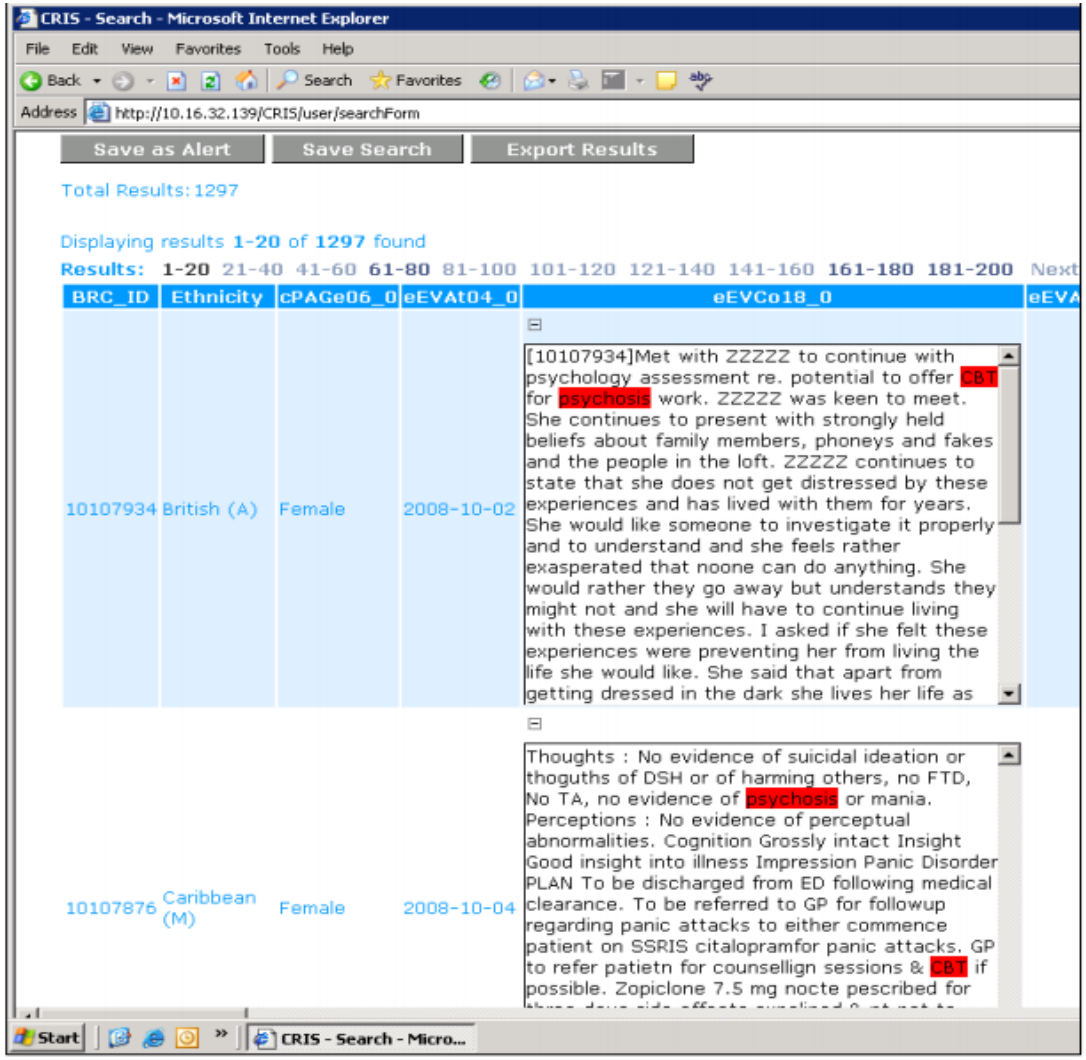
The front-end CRIS was particularly useful in exploring data on a descriptive level, for data presented in this thesis. It enabled basic cohort checks, such as the total OUD sample in a given observation period; completeness of data for particular scales, such as the BRSA-A or

HoNOS in the OUD cohort; and localizing and exploring the availability and quality of available variables specific to addiction services for subsequent analysis.

The front-end CRIS was also frequently used in collecting missing information, which could not be extracted using more complex tools or data linkages described further below, or instances where manual free-text coding was the only possibility to extract necessary information. For example, as described in Chapter 4 where a manual text search was carried out to establish causes of death for those individuals where this information was not available through a linkage to ONS data, or in instances where patients' reasons for ending their treatment in SLaM needed defining, as described in detail in Chapter 6.

The front-end CRIS however, is a much a simplified format of CRIS. Problems arise when searches requires complex extraction planning and handling of large data - for example, when using large samples, where reading through individual notes is not feasible, or when extracted data from the free-text fields must take into account the linguistic context rather than a simple key word search. Front end CRIS can search and retrieve data but is limited by using basic Boolean operators (and/or/not), therefore it cannot perform relational searches. Externally linked data, such as cause-specific mortality, is not available for retrieval via the front-end CRIS either. The back-end CRIS, also known as CRIS SQL, was therefore developed for such data explorations; and was essential to conduct analysis presented in this thesis; and is described below.

Figure 3.1 Screen-shot of front-end CRIS results table (Stewart et al., 2009).



- Step 1: Records were searched for the terms 'CBT' and 'Psychosis' entered into free text case notes.
- Step 2: Ethnic category, sex, the date of relevant events and the text of the case themselves were brought back in the results table

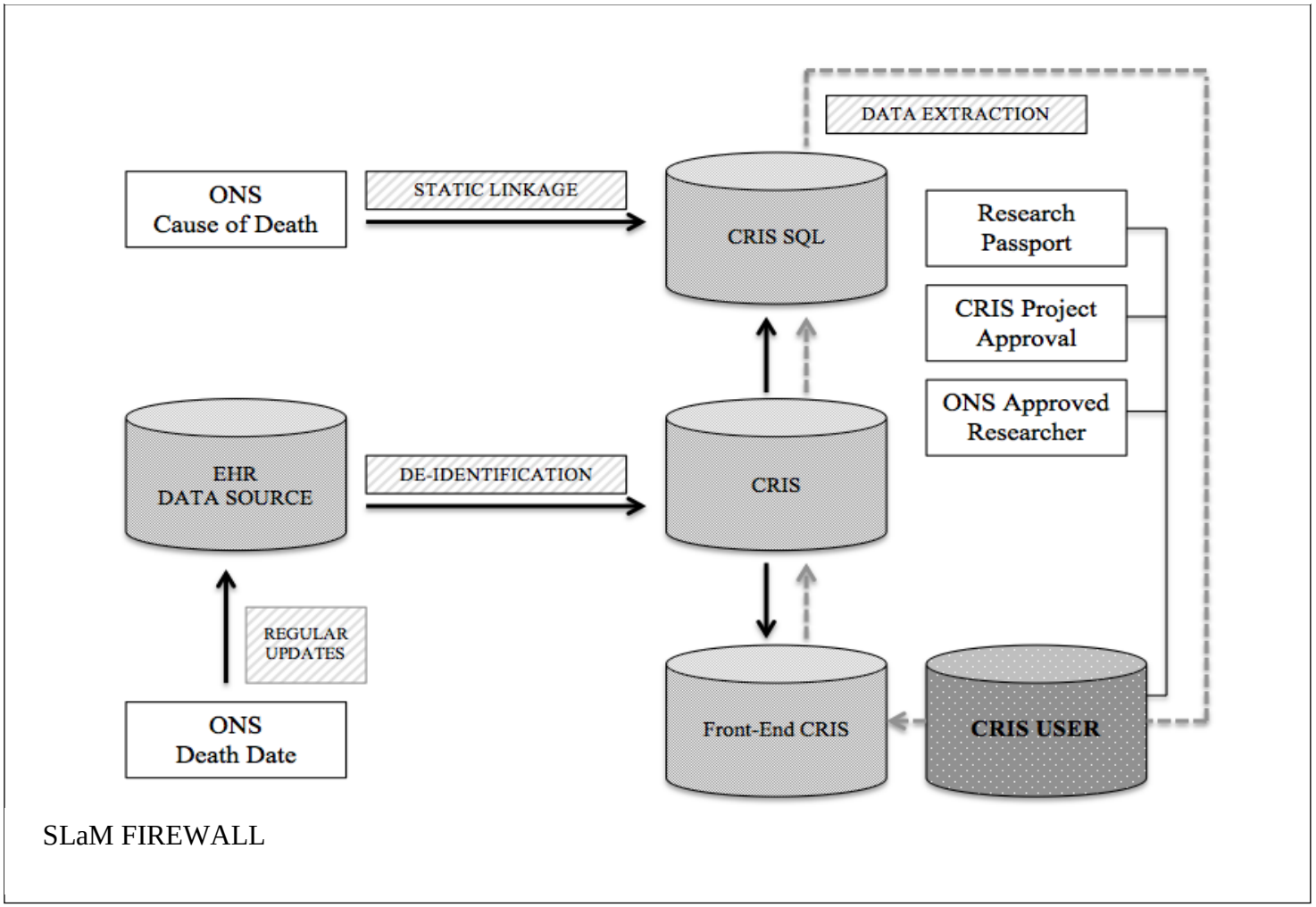
.

3.3.4 CRIS SQL

Structured Query Language (SQL) was the key 'language' for interacting with the CRIS database and for extraction of data used in this thesis. SQL can handle complex queries, which may include multiple sources of information and relational searches. Data extraction (see appendix v. for an example of data extraction used in Chapter 5) using SQL can search and retrieve information from source structured electronic health records, from internally and externally linked data and access data which has been coded using NLP software taking into account the linguistic context in free-text fields (described below). Data presented in Chapter 4, for example, required CRIS SQL to include: a) NLP to extract OUD diagnoses from free-text fields (in addition to information derived from their designated structured fields); b) externally linked cause-specific mortality data to identify those who had fatal overdose; c) relational search where deprivation score, for example, was recorded closest to the recorded variable of interest; or prescription of medication within given period *after* a variable of interest was recorded for each patient.

Effective utilisation of CRIS, its applications, location and quality of available variables, its limitations, linked data and data extractions required development of a close working relationship with the bioinformatics team who provided advice and assistance in planning, handling and extraction of datasets for analyses in this thesis. Development of good relationships with clinicians, especially within addictions, was also required, who were able to direct me towards efficient identification and localisation of variables of interest within ePJS and CRIS. Both CRIS front-end and SQL training were also undertaken to understand and plan data extraction and to better communicate with the CRIS team. The full operational model visualising both front-end and SQL CRIS is presented in Figure 3.2, including regularly updated and static data linkages explained below.

Figure 3.2 CRIS Operational Model



3.3.5 NATURAL LANGUAGE PROCESSING

Anecdotally, it is said that up to 70% of the information content of patient records is in free text form and accessing this information is a priority for health research[1]. NLP techniques have an important role to play, particularly for mental health patient records where text fields are often substantial and contain some of the most important clinical information (Ford et al., 2016; Névéol et al., 2016; Perera et al., 2015). Traditionally, extracting free-text information has required manual coding, where the researcher reads the free-text and codes it by hand according to a defined set of coding rules (Perera et al., 2015; Stewart et al., 2009). In this study, the traditional method was used in extracting some variables in small subsets of the data, described in more detail in Chapters 4 and 6. However, it is near impossible to manually code free text fields on a large scale due to time and labour constraints.

NLP data extractions can be carried out in a timely, efficient and reliable manner. General Architecture for Text Engineering (GATE) - open source software developed since 1995 at the University of Sheffield, is a leading suite of tools that facilitate the use and development of NLP applications and features and was chosen as the core NLP infrastructure for CRIS. NLP applications to date have brought in new and hitherto inaccessible data on cognitive function, education, social care receipt, smoking, diagnostic statements and pharmacotherapy and some of these are briefly described below.

[1] Retrieved from http://openminted.eu/1129-2/

The first NLP application to be developed was for the MMSE (The Mini Mental State Examination), a commonly used 0–30-point assessment of global cognitive function. The objective of the application was to ascertain both the numerator and denominator scores (because denominator scores of less than 30 are used where some items cannot be attempted because of e.g. sensory impairment), as well as the date implied for the assessment (because clinical text fields commonly refer to previous as well as current scores). The application was tested on 100 patients with high precision and recall scores (97% and 98% respectively) (Su et al., 2014).

A number of other NLP applications have since been developed, including an application for educational attainment which sought to ascertain the numeric value associated with text commenting on school leaving age, whether the age itself or the year (precision 95%; recall 59%) and an application for 'living alone' which sought to identify that phrase or equivalents applied to the patient (precision 93%; recall 99%) (Perera et al., 2015).

In developing the smoking application, authors extracted information from open-text fields, classifying patients as either 'currently smoking', 'past smoker' or 'has never smoked', with smoking of substances other than tobacco (e.g. marijuana/cannabis and cocaine) specifically excluded (Wu et al., 2013). The methodology used an iterative process of manual 'gold standard' annotation of free-text documents, followed by comparison with the results generated by the application at each development stage, with analysis of this comparison feeding further development of the rules. The smoking application was tested on 100 patients with 93% precision and 58% recall scores. The smoking status using this NLP application was extracted for data described Chapter 4, however, the variable was excluded from analysis for reasons described within the same chapter.

The application for ‘diagnosis’ sought to extract any text strings associated with a diagnosis statement in order to supplement the existing structured (ICD-10) fields. Its performance was evaluated formally in a random sample of 75 documents for ‘vascular dementia’ (Sultana et al., 2014), but it is recommended for individual further evaluation in other conditions. The ‘diagnosis’ application was used frequently in this project and my own precision validation for the OUD cohort is described in the ‘Core Variables’ section below.

NLP applications for pharmacotherapy have also been developed, using a gazetteer of generic and commercial names for all medications in UK use in order to ascertain instances where the patient was reported as receiving these, with supplementary rules for ascertaining recorded dose, frequency/timing and starting/stopping statements. Its precision was first tested for clozapine receipt against a manual search of 279 documents and recall was ascertained on a random set of 200 documents containing the word clozapine and scrutinised to ascertain an actual prescription (Hayes et al., 2015). NLP applications have recently been extended to cover a range of affective and psychotic symptoms, allowing much more detailed phenol-typing of large samples than a diagnosis alone provides (Patel et al., 2015a; Patel et al., 2015b) and a range of adverse drug events have also recently been successfully captured (Iqbal et al., 2015). Additionally, for all evaluations, an F-statistic was calculated, representing the harmonic mean of precision and recall and defined as: $F=2\times(precision\times recall/(precision+recall))$. More detailed description and performance data for NLP applications are beyond the scope of this thesis but are summarised in Perera et al., (2015).

3.4 CORE VARIABLES

Although data-specific variables will be described in their designated chapters, it is useful to specify the key variables here, for clarity and completion of the data-source information.

3.4.1 DIAGNOSES

Diagnoses in SLaM (and subsequently in CRIS) are a mandatory field and are recorded in accordance to the ICD-10 (WHO, 1993). Opioid use disorder patients in SLaM are therefore retrieved in data extractions if they have been diagnosed with a primary or secondary IC-10 – F11 opioid use disorder. Additionally, OUD diagnoses were searched using the 'diagnosis' NLP application discussed earlier in this chapter, to supplement data unavailable in structured field search/extraction (usually secondary diagnoses) in Chapters 4-7. Furthermore, in Chapter 4, the NLP diagnoses application was also used to extract psychiatric comorbidity diagnoses for severe mental illness, personality disorders and alcohol use disorder.

The NLP application for 'diagnosis' sought to extract any text strings associated with a diagnosis statement in order to supplement the existing structured (ICD-10) fields. As explained earlier, above, its performance was evaluated formally in a random sample of 75 documents for 'vascular dementia' (Sultana et al., 2014) with precision and recall of 99% and 98% respectively, but is recommended for individual further evaluation in other conditions. Therefore, additional precision testing was carried out for this cohort in 50 randomly selected patients whose diagnosis were extracted via GATE. The precision for the 'diagnosis' NLP application for this cohort was 98%.

3.4.2 ALL-CAUSE MORTALITY

NHS number is a unique identifier for UK NHS records. All death certifications are linked to this identifier at national level and health service providers are required by law to keep records up to date with respect to this. Every death in the UK, after the issuing of a formal death certificate, must be reported to the Office for National Statistics General Records Office (ONS–GRO) and conveyed to the NHS Care Records Service, which holds these death notifications and makes them available to all NHS organisations. In accordance, on a monthly basis, SLaM downloads a list of deceased patients from the NHS Care Records Service and updates their dates of death onto patients' records. This process applies to both active and non-active (i.e. discharged or deceased) patients present on the ePJS system.

3.4.3 CAUSE-SPECIFIC MORTALITY

The CRIS database is also linked with external data sources, such as the Hospital Episode Statistics (HES) and the National Pupil Database and Primary Care database (Lambeth DataNet). Such record linkages are performed via a personal identifiers matching process, are de-identified at linkage, and are available to BRC researchers in an anonymised form. In this study, I was able to establish causes of death via data linkage with the ONS, which collects information on cause of death from civil registration records. For registered deaths, the underlying cause of death is derived from the sequence of conditions leading directly to the death and is recorded on the death certificate. The death registration also records a list of other conditions or diseases that the patient had at the time of death, which may or may not have directly contributed to the death.

Deaths are subsequently coded in line with the ICD and, at request (with appropriate approvals), provided to the BRC for anonymised CRIS linkage. All researchers, including myself, are required to obtain ONS Approved Researcher approval before handling ONS linked data. The ICD-10 diagnostic codes, as extracted within the subsequent chapters, as pertaining to specific causes refer only to those codes that are present in that specific dataset, and hence, might not include a 'complete list' of the cause specific ICD-10 F-codes.

However, cause of death data is a static data linkage, with irregular updates (unlike all-cause mortality data). Each update request requires a number of administrative tasks from both the SLaM linkage team and the ONS team, resulting in severe delays. Furthermore, ONS reports an approximate 6-month to one year delay in establishing causes of death (ONS, 2011). These delays require analytical period adjustments at extraction-level to avoid constructing data sets with excessive amounts of missing data corresponding to the most recent deaths.

As described earlier, in some cases, for example where a death date is present but no underlying ICD-10 cause of death code was provided, I would go back to the event notes using front-end CRIS, then search and retrieve information on cause of death if available. This technique was carried out for data described in Chapter 4, but not in data presented in subsequent chapters. Whilst I was able to match the BRC IDs in front-end CRIS for those missing cause of death in Chapter 4, the ONS security model changed, requiring annonymization of the BRC IDs for datasets including ONS cause specific mortality. Subsequently, this prevented me from searching through front-end CRIS for missing causes of deaths in Chapters 5-7 and hence I needed to solely rely on causes of deaths provided by the ONS. The last date of death available in the ONS death data is 12 April 2015; therefore,

deaths occurring after this date will not have an underlying cause of death code assigned to them unless a more recent update is requested, approved and performed.

3.5 DATA SOURCE LIMITATIONS

The CRIS tool provides researchers with access to a long running system of fully electronic clinical records, allowing in-depth secondary analysis of numerical, string and free-text data, whilst preserving anonymity through technical and procedural safeguards. However, there are some limitations to CRIS data source that must be acknowledged before moving on to study-specific limitations discussed in their designated chapters.

First, the completeness of data in CRIS relies on information entered by the NHS staff. Often, designated structured fields are not utilized by clinicians, rather information is typed in free-text fields, resulting in difficulties in capturing this information using the CRIS front-end. Essentially, CRIS relies on clinicians completing electronic forms and fields fully and in addition to free-text, which is not often the case. Although a range of NLP applications are in place to extract information from free-text, these are variable-specific and limited to those features in the text considered high priority for the research undertaken to date. The development of new applications is extremely complex and labour intensive, for example, as that described by Kadra and colleagues (2015).

Second, SLaM provides a variety of mental health services and ePJS is an extensive database. The internal procedures for completion of electronic data often vary between Clinical Academic Groups (CAGs) within SLaM, with different views on the relevance of recorded information across the diagnostic groups. A good example of this is the completion of the HoNOS. HoNOS is a standard measure of patient wellbeing, widely used in UK mental health services, completed by clinicians after routine assessments (Wing et al., 1998). Across a number of diagnostic groups the completion of HoNOS scale is relatively high - 83% of all SLaM patients with schizoaffective disorder (ICD-10 F25) and 63% of SLaM patients with

(ICD-10 F33) major depressive disorder have HoNOS completed. In my OUD cohort however, the HoNOS completion rate was only 14%. This is because alternative and addiction-specific measures exist, therefore this information is captured elsewhere. On the other hand, information sources, such as the NDTMS or the Brief Risk Assessment Scale (which are specific to addictions), are completed at high rates by the addictions staff (91% and 84% respectively), completion of which would have little relevance in other CAGs.

Aside from CAG differences in the type of information recorded, problems arise with multiple structured fields for recording the same or similar information. A good example of this is information relating to prescribing, where relevant information was found in five different locations in ePJS. These include various structured fields and through 'pharmacotherapy' NLP free-text searches. This issue was particularly problematic in establishing end of treatment dates in the current cohort, and is further described in Chapter 6. Therefore, a great deal of time was spent in familiarising myself with the ePJS and CRIS, developing close working relationships with the bioinformatics team, and clinicians who use ePJS daily and were able to direct me towards variables and information I needed so that no information was missed or misinterpreted.

Data linkages, while increasing the richness of available data, can also present their own set of challenges. For example, as described earlier, the static ONS-CRIS cause of death data linkage results in update delays, requires adjustments in observation windows, and contains missing data. Performing new data linkages is also a long and complex process, from technical as well as ethical perspectives. For example, during this PhD I tried to perform data linkage between CRIS and London Ambulance Services (LAS) so that data on fatal as well as non-fatal opioid overdose call-outs could be captured for analysis. This, however, has proven

unsuccessful due to the type and volume of approvals required, time constraints, and the type of electronic and quality of data available from the LAS.

Finally, treatment provision in SLaM Addiction services is extensive and complex. SLaM addictions treatment provisions include inpatient services, specialist prescribing services, complex case services, community drug and alcohol treatment (CDAT) services, and supervised injecting services. In addition, SLaM addictions services work in close partnership with the GP (general practice) shared care services, the dual-diagnosis team, and a number of third party/charity sector service providers. Patients, especially opioid dependent patients, enter, drop out, re-enter and transfer between services or prison frequently, therefore capturing one's complete journey through services is problematic. This is primarily because these additional services are not electronically connected with ePJS or CRIS and valuable data is often lost to follow-up with each drop out or transfer. Treatment information beyond transfer involves sporadic mentions in event notes or correspondence and requires manual retrieval. Where a patient is involved in the shared care team, he or she may be regularly seen by the SLaM CDAT for psychological assessment or relapse prevention modalities, but their prescription may be provided through his or her GP. In this situation, prescription details may be incomplete and only sporadically mentioned in the notes, rather than their designated ePJS fields. However this situation can be addressed to some extent though searching and reading patient documents using the CRIS front end since correspondence to and from GP is recorded on the system.

CHAPTER 4 PSYCHIATRIC COMORBIDITY AND MORTALITY

The contents of this chapter has contributed to the following:

Publication in a peer-reviewed journal:

Bogdanowicz, K.M., Stewart, R., Broadbent, M., Hatch, S.L., Hotopf, M., Strang, J., Hayes, R. (2015). Double Trouble: Psychiatric Comorbidity and Opioid Addiction – all-cause and cause-specific mortality. Drug and Alcohol Dependence, 148: 85–92.

Bogdanowicz, K.M., Stewart, R., Broadbent, M., Hatch, S.L., Hotopf, M., Strang, J., Hayes, R. (2014). Psychiatric comorbidity and excess all-cause and cause-specific mortality in opioid addicts. Alcohol & Alcoholism, 49:1 (published abstract).

Oral presentations at international conferences:

Bogdanowicz, K.M. **(presenting author)**, Stewart, R., Broadbent, M., Hatch, S.L., Hotopf, M., Strang, J., Hayes, R. Opioid use, Mortality and the Influence of Psychiatric Comorbidity and Psychological Health; European Psychiatric Association Section of Epidemiology and Social Psychiatry Meeting; Ulm, Germany; May 2014.

Bogdanowicz, K.M. **(presenting author)**, Stewart, R., Broadbent, M., Hatch, S.L., Hotopf, M., Strang, J., Hayes, R. Double Trouble: Psychiatric Comorbidity and Opioid Addiction – all-cause and cause-specific mortality; International Federation for Psychiatric Epidemiology; Bergen, Norway; October; 2015

4.1 SUMMARY

Introduction: Opioid misusers have recognized high mortality but the influence of psychiatric comorbidity in excess cause-specific mortality is unclear, with existing literature reporting mixed or limited results.

Aim: The aim of the analysis presented in this chapter was to investigate the associations between subjective ratings of psychological health - a proxy measure of depression and anxiety, comorbid diagnosis of PD, SMI and AUD, in relation to all-cause and cause-specific mortality in OUD patients.

Methods: OUD patients were identified in the SLaM case register within the observation period between 1st April 2008 and 31st December 2012. Deaths were identified through database linkage to the national mortality dataset. Standard mortality ratios (SMR) were calculated to compare mortality risk with the general population. Cox and competing risk regression models were used to investigate the effect of psychiatric comorbidity and psychological health on all-cause and cause-specific mortality (respectively).

Results: Of 4,837 OUD patients, 176 had died. Mortality rates were substantially higher than in the general population (SMR 4.23; 95% CI 3.63-4.90). Among those with OUD, comorbid personality disorder and comorbid alcohol use disorder was associated with increased all-cause mortality in all models, including the fully adjusted model, controlling for socio-demographic factors, severity of drug use factors, risk behaviours and physical health (HR 2.15, 95% CI 1.17–3.95; HR 2.28, 95% CI 1.54–3.36).

AUD was associated with increased risk of fatal overdose (SHR 2.53, 95% CI 1.14 – 5.61) and liver-related deaths (SHR 7.28, 95% CI 2.65–19.97). Individuals with OUD and

comorbid PD had almost four times greater risk of liver-related deaths compared to those without comorbid PD (SHR 3.82, 95% CI 2.65–10.46). Comorbid severe mental illness and poor psychological health were not associated with increased mortality in these analyses, and the potential reasons for non-significant results are discussed.

Conclusions: This study finds elevated risks of mortality for OUD patients with comorbid personality disorder and alcohol misuse, thereby highlights the importance of assessment for PD and AUD in patients with OUD in order to identify individuals at substantially elevated mortality risk and subsequently, to enable a more personalized approach to their medical care.

4.2 INTRODUCTION

4.2.1 EXISTING LITERATURE

Opioid dependent individuals are at substantially higher risk of mortality compared to the general population, to those with other drug-use problems (Harris & Barraclough, 1998; Hayes et al., 2011), and to people with SMI (i.e. psychotic disorders and bipolar affective disorder) (Chang et al., 2010; Dickey, 2004; Harris & Barraclough, 1998). Previous research found that individuals with substance use disorders, especially opioid dependence, have more than four times the expected risk of mortality, with life expectancies reduced by more than nine years compared to national norms. This difference was most pronounced in females whose life expectancy was reduced by more than 17 years (Hayes et al., 2011).

Although there is evidence of the link between opioids and elevated mortality risk, factors which may predispose some opiate users to higher or lower mortality risk compared to their peers with the same disorder are not properly understood.

Substance use disorders are strongly associated with other psychiatric disorders in both clinical (Brooner et al., 1997; Weaver et al., 2003) and population samples (Rodrigues-Llera et al., 2006). Lifetime comorbidity with other psychiatric disorders range from 44% and 93% (Brooner et al., 1997; Cacciola et al., 2001; Khantzian & Treece, 1985; King et al., 2000; Krausz et al., 1999; Mason et al., 1998).

Psychiatric comorbidity is associated with poor treatment prognosis, greater psychosocial impairment, increased risk of relapse and higher rates of HIV risk behaviour (Arendt et al., 2007; Brooner et al., 1997; Darke & Ross, 1997; Disney et al., 2006; Landheim et al., 2006;

Rounsaville et al., 1986; Rounsaville et al., 1982). Comorbid alcohol problems are also highly prevalent in this patient population (25%) (Gossop et al., 2002) and are reportedly associated with an increased risk of fatal overdose (Darke & Ross, 1997). Mood and anxiety problems (41%), personality disorders (PD) (40%) and psychotic disorders (12%) are found to be the common comorbid diagnosis not only in opioid users (Rodriguez-Llera et al., 2006) but also in other drug users (Weaver et al., 2003). Antisocial PD is a rare diagnosis in the general community (4%) (Robins, 1991), but occurs at rates of up to 65% in heroin-using samples (Bargagli et al., 2007; Darke et al., 1994).

In addition, people with a diagnosis of PD have a four-fold higher mortality, with substantially reduced life expectancy (Fok et al., 2012). Similarly, substantially higher mortality rates are found in people with SMI and depressive disorders when compared to the general population (Chang et al., 2010). In spite of this, the impact of psychiatric comorbidity on mortality risk in substance use disorders has received only moderate attention, with existing investigations reporting mixed results (as discussed in more detail in Chapter 2) (Arendt et al., 2011; Gossop et al., 2012; Mattison et al., 2011), which rarely investigate beyond overdose deaths (Johnson et al., 2015).

4.2.2 AIMS AND HYPOTHESIS

Given the high prevalence of comorbid alcohol, mood problems, PD and SMI among opioid users, and particularly high hazard ratios for mortality risk in individuals with these diagnosis, it is plausible that these psychiatric problems may contribute to the elevated mortality risk observed in this patient group, with regard to both natural and unnatural causes of death.

Investigating the impact of comorbid psychiatric problems in opioid users and looking beyond unnatural causes of mortality may help improve our understanding of the pathways to premature mortality among opioid users as well as identifying subgroups at substantially elevated mortality risk.

I used the large and well-established SLaM case register (Stewart et al., 2009) (described in Chapter 3) to explore these relationships more fully. From analyses of the data described in this chapter, I investigated the associations between subjective ratings of psychological health, such as feelings of depression and anxiety, comorbid diagnosis of PD, SMI and AUD, in relation to all-cause as well as cause-specific mortality, in a large cohort of opioid-dependent patients receiving secondary mental healthcare.

4.3 METHOD

4.3.1 STUDY SETTING

This investigation was set within SLaM - one of the largest specialist mental healthcare services in Europe, which provides, within the framework of the NHS, comprehensive mental healthcare and addiction services to a catchment population of approximately 1.2 million residents. Data for this investigation was obtained using the CRIS system – a SLaM based de-identified database, developed by the NIHR BRC and Dementia Unit, which allows researchers to search and retrieve thousands of patient records in a de-identified form. A detailed description of the study setting, including SLaM and addictions services, and a detailed account of the CRIS system is explained earlier (Chapter 3). Investigation specific variables were initially explored using the front-end CRIS, and a detailed data extraction plan was created in accordance with the requirements and advice from the bioinformatics team, who extracted the full data set for these analyses.

4.3.2 INCLUSION CRITERIA

Diagnoses in CRIS are coded according to the ICD-10 (WHO, 1993) (see Chapter 3 for extended details). Diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using NLP. The NLP application for 'diagnosis' (explained and validated in Chapter 3) sought to extract any text strings associated with a diagnosis statement in order to supplement the existing structured fields.

In this analysis, the sample comprised a cohort of 4,837 SLaM patients who were diagnosed with an ICD-F11 OUD within the period between 1st April 2008 to 31st December 2012 and

who had been assessed by a clinician using the NDTMS and the TOP (Marsden et al., 2008) (see appendix vi.) at least once during the observation period.

All drug treatment agencies are required to provide a basic level of information to the NDTMS on their activities each month. The TOP is a reliable and valid 20-item instrument for monitoring substance misuse treatment outcomes and is designed to capture pertinent features such as substance use, health risk behaviour, offending, health and social functioning; and both NDTMS and TOP are now firmly embedded in the routine in-treatment monitoring of outcomes across the UK. In the SLaM case register, OUD was the second most frequently diagnosed substance use disorder after AUD (Hayes et al., 2011); and approximately 96% of SLaM patients with an OUD (within the observation period) appeared on the NDTMS completed, and 89% had the TOP completed on at least one occasion.

4.3.3 MAIN OUTCOME MEASURES

The main outcome in this study was all-cause and cause-specific mortality, within the period 1st April 2008 to 31st December 2012 (inclusive), in individuals with primary or secondary OUD. Routine mortality identification is performed on a monthly basis by SLaM through a linkage to the national mortality base using the unique NHS number assigned to all UK citizens. This mortality tracing allowed me to establish who had died during the observation period and includes active as well as non-active SLaM cases.

In addition, a linkage to data specifically derived from death certificates allowed me to establish the recorded underlying cause of each death. The full procedure for identifying and confirming SLaM patient deaths and cause-specific mortality data linkage has been described

in Chapter 3. In this investigation, based on death data extracted within the current cohort, ICD-10 codes A00-B99 were classified as infectious diseases; codes C220, K703-K769 were classified as alcoholic and other hepatic diseases; codes C349, J13-J449 were grouped as pneumonia and other pulmonary diseases; codes V01-Y98 were classified as unnatural causes, with codes X420-X450, Y120, Y125 sub-classified as overdose deaths. The remainder of ICD-10 cause of death codes within this cohort related to other natural causes of mortality and were classified as such. These groupings were based on the most common causes of mortality in this patient group to increase power for multivariable analysis.

4.3.4 EXPLANATORY VARIABLES

Exposures of interest

The main characteristics of interest in this study were psychological health and psychiatric comorbidity, measured by investigation of four aspects of mental health, including patients' subjective psychological health ratings (a proxy measure for depression and anxiety), and comorbid diagnosis of a SMI, PD and AUD.

Psychological health rating data was extracted from the TOP, which is a reliable and valid 20-item instrument for monitoring substance misuse treatment outcomes and is designed to capture pertinent features such as substance use, health risk behaviour, offending, health and social functioning (Marsden et al., 2008). Psychological health rating is the patient's subjective rating of psychological health status, such as feelings of anxiety, depressive symptoms and other emotional problems measured by a single 21-point scale (0, 'poor' to 20, 'good').

Cohort members were classified as having a comorbid diagnosis of SMI if they had received at least one of the following diagnoses during the observation period: schizophrenia (ICD-F20), schizoaffective disorders (ICD-F25), and bipolar affective disorder (ICD-F31). These were collapsed together to increase power.

Similarly, the cohort was classified as having a comorbid diagnosis of PD if they had received either a specific personality disorder (ICD-F60) or mixed and other personality disorder diagnosis (ICD-F61), and a comorbid diagnosis of AUD if they had received an ICD-F11 alcohol use disorder diagnosis.

Consequently, those with more than one comorbid diagnosis could appear in more than one category. As in inclusion criteria, psychiatric comorbidity diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using NLP to supplement the structured fields.

Potential confounders

In addition to the main exposures of interest, an extensive list of other covariates derived from TOP and NDTMS were considered as potential confounders. Date of birth, ethnicity and gender are routinely recorded on SLaM electronic patient records in their designated fields. Age was calculated from the date on which individuals received their ICD-F11 OUD diagnosis within the observation period. Ethnic classifications were condensed into "White

British", "Other White background", "African, Caribbean and other black background", and "Mixed, unknown and other".

The level of deprivation for the neighbourhoods was established by linking the patient's residential postcode to the UK Census data projected for 2007, as reported by Hayes and colleagues (2012). More specifically, the index of multiple deprivation was used to give a summary of the overall socioeconomic status at the level of lower super output area (LSOA). Each LSOA contains a minimum of 1000 residents and 400 households, but with an average of 1500 residents. The index of multiple deprivation is derived from multiple domains of deprivation including: employment, income, education, health, barriers to housing and services, crime and the living environment. Each domain is given a specific weighting, in accordance with Noble and colleagues (Noble et al., 2007), to reflect its overall importance in the calculation of this index. Moreover, each domain is made up of a number of specific indicators that reflect different aspects of the deprivation they are intended to measure. Increasing scores in the index of multiple deprivation are indicative of more severe deprivation level. In this analysis the address that was recorded closest in time to April 1, 2008 for each patient was used to calculate deprivation scores, which were then divided into tertiles.

Severity of drug use was extracted from NDTMS and TOP and included 'age at first primary problem drug use', frequency of opiate use in the past 28 days and a total number of different drugs used, collapsed from both sources. Injecting behaviour was collapsed into a binary variable using information from both the NDTMS (administration route data e.g. oral, intravenous, inhalation) and from TOP (frequency of injecting administration in the past 28 days). Physical health, extracted from TOP, was the patient's subjective measure of physical

health, such as symptoms and being bothered by illness, recorded using a single 21-point scale (0, 'poor' to 20, 'good'). Likelihood ratio tests indicated that it was acceptable to include psychological health rating, age at first diagnosis, level of deprivation, frequency of opiate use and the total number of different drugs used as continuous variables in the statistical analyses.

Using NLP applications, I also extracted 'smoking status' and 'living alone' data for this cohort, for inclusion as potential confounders. However, these variables were not included in the analyses due to large numbers of missing values. The NLP application, searching free text annotations to establish patient's 'smoking status' (current, past or never), only returned data for 4.32% of patients (n=209 / 4837). This poor recording of patients smoking status within addiction was not surprising, as previous research identified that staff rated smoking treatment significantly less important than treatment of other substances and only 29% of staff thought it should be addressed early in a client's primary addiction treatment (Cookson et al., 2014).

The NLP application to establish whether the patient was living alone at the time of their OUD diagnosis was slightly better compared to smoking status, returning data for 66% (n=3193 / 4837), leaving 34% of missing data.

4.3.5 Statistical Analysis

I calculated SMR using indirect standardization in STATA 12 for the period between 1 April 2008 to 31 December 2012. The numerator was the number of deaths observed in SLAM records within the observation period and the denominator was the number of deaths one

would expect to occur over the observation period based on age and gender specific death rates for the England and Wales population in 2008 (ONS, 2009). SMRs were age-standardised using 5-year age bands and stratified by gender, and are presented in Table 4.2. Cox regression (Cox, 1972) for survival analysis was used to model the associations of psychological health and psychiatric comorbidity with all-cause mortality. Competing risk regression was performed to model cause-specific mortality in the current cohort.

Each individual patient's 'at risk' period commenced from the date of their first OUD diagnosis within the observation period between 1 April 2008 to 31 December 2012 and ended on the day of their death or the end of observation period for individuals who survived.

Associations between psychological status/comorbidity (psychological health rating, comorbid SMI, comorbid PD, comorbid AUD) and all-cause mortality were estimated after adjusting for the following blocks of variables: (i) age at diagnosis and gender, (ii) socio-demographic factors (age at diagnosis, gender, ethnicity, deprivation level, relationship status), (iii) age at diagnosis, gender and severity of drug use (age at first use, frequency of opiate use in past 4 weeks, total number of drugs used); (iv) age at diagnosis, gender and risk behaviours (intravenous drug administration); (v) age at diagnosis, gender and physical health; (vii) adjusted for all of the above, including the principal exposures of interest (fully adjusted model).

Furthermore, associations with overdose deaths, hepatic disease deaths (two largest sub-cohorts), and all other causes of deaths; and psychological well-being were calculated using competing risk regression models. Interactions between mortality and age and gender were also tested. All variables used in this analysis are listed in Table 4.1.

4.4 RESULTS

4.4.1 COHORT CHARACTERISTICS

The characteristics of the sample are reported in Table 4.1. The total number of individuals extracted from CRIS who met the inclusion criteria was 4,837 (71% male; 68% "White British"), with 176 deaths registered within this cohort. Patients contributed a total of 14,782 person years at risk. Age at diagnosis within the observation period ranged from 14 to 86 years with a mean age of 37.5 years (although this may not have been patients' first approach to addiction services over their lifetime). Individuals diagnosed aged 70 and over (n=15) were primarily diagnosed for medical reasons and/or were in OUD treatment prior to April 2008 (i.e. prior to start of analytical observation period).

Table 4.1 Cohort characteristics (n=4,837).

Variables	Number of individuals (%)	Number of deaths (%)
Total	4837	176 (4)
PSYCHIATRIC WELL-BEING		
Psychological Health Rating (0-20, in tertiles)		
Poor (0-8)	1318 (27)	57 (32)
Moderate (9-12)	1477 (31)	49 (28)
Good (13-20)	1452 (30)	39 (22)
Missing	590 (12)	31 (18)
Comorbid SMI disorder		
No	4500 (93)	162 (92)
Yes	337 (7)	14 (8)
Comorbid personality disorder		
No	4564 (94)	159 (90)
Yes	273 (6)	17 (10)
Comorbid alcohol use disorder		
No	3860 (80)	109 (62)
Yes	977 (20)	67 (38)
SOCIO-DEMOGRAPHIC VARIABLES		
Age group at first F11 diagnosis		
14-24	415 (9)	8 (5)
25-29	693 (14)	12 (7)
30-34	872 (18)	26 (15)
35-39	949 (20)	37 (21)
40-44	938 (19)	31 (18)
45+	970 (20)	62 (35)
Missing	0	0
Gender		
Female	1404 (29)	46 (26)
Male	3433 (71)	130 (74)
Ethnicity		
White British	3266 (68)	140 (74)
Other White	595 (12)	22 (13)
Black	516 (11)	10 (6)
Mixed, unknown & other	460 (10)	4 (2)
Level of deprivation (0-100, in tertiles)		
Low (2.6 - 28.5)	1362 (28)	41 (230

Moderate (28.6 - 38.2)	1376 (28)	54 (31)
High (38.3 +)	1393 (29)	56 (32)
Missing	706 (15)	25 (14)
Relationship status		
Not in a relationship	4215 (87)	163 (93)
In a relationship	390 (8)	9 (5)
Missing	232 (5)	4 (2)
SEVERITY OF DRUG USE		
Age group at first use		
0-14	378 (8)	17 (10)
15-19	1391 (29)	69 (39)
20-24	948 (20)	20 (11)
25-29	578 (12)	14 (8)
30+	754 (16)	28 (16)
Missing	788 (16)	28 (16)
Days of opiate use in past 4 weeks		
None	1534 (32)	62 (35)
1-27	1337 (28)	36 (20)
Everyday	1398 (29)	48 (27)
Missing	568 (12)	30 (17)
Total number of different drugs used		
1	848 (18)	34 (19)
2	1398 (29)	50 (28)
3	1349 (28)	52 (29)
4+	1242 (26)	40 (23)
RISK BEHAVIORS		
Injected		
Not injected	3227 (67)	92 (52)
Injected	1382 (29)	72 (41)
Missing	228 (5)	12 (7)
PHYSICAL HEALTH		
Physical health status (0-20, in tertiles)		
Poor (0-9)	1283 (27)	79 (45)
Moderate (10-13)	1451 (30)	42 (24)
Good (14-20)	1514 (31)	24 (14)
Missing	589 (12)	31 (18)

4.4.2 MORTALITY IN OPIOID USE DISORDER AND THE GENERAL POPULATION

Mortality rates in this cohort were substantially higher than in the general population (Table 4.2) (SMR 4.23; 95% 3.63-4.90), especially for women with OUD where rate was over five times the general population (SMR 5.69; 95% CI 4.16-7.59). To explore this elevated risk in more detail I proceeded to identify specific factors associated with mortality in this cohort.

Table 4.2 Indirect age-standardised mortality ratios stratified by gender for opioid use disorder diagnosis in SLAM compared to population of England and Wales in 2008.

	n	**Expected deaths**	**Observed deaths**	**SMR (95% CI)**
Total	4837	41.6	176	4.23 (3.63 – 4.90)
Female	1404	8.1	46	5.69 (4.16 – 7.59)
Male	3433	33.6	130	3.87 (3.24 – 4.60)

4.4.3 ALL-CAUSE MORTALITY IN OPIOID USE DISORDER

The proportional hazard assumptions for Cox survival analysis were checked with no significant interactions between mortality, psychiatric comorbidity and time. Table 4.3 summarizes findings from initial Cox regression models of factors potentially associated with all-cause mortality in patients with OUD. Associations between psychological health and all-cause mortality remained the same after adjustment for age and gender. Better psychological health status was protective (HR 0.96, 95% CI 0.92 - 0.99, per unit increase in the psychological health status scale), while those with co-morbid PD and AUD were at increased risk of mortality after age and gender adjustment (adjusted HR 2.04, 95% CI 1.23-3.36; HR 2.42, 95% CI 1.77-3.28).

No associations were found between severe mental illness and mortality. Age at diagnosis, increased level of deprivation, and injecting drug administration were also all associated with an increased risk of mortality in the age and gender adjusted models. Initiation of drug use between ages 20 to 24 was associated with decreased mortality risk when compared to younger age at first use. Similarly, being in a relationship, good/moderate physical health and ethnicity other than white were associated with a decreased mortality risk.

Table 4.4 displays Cox regression associations between psychiatric co-morbidities and all-cause mortality after controlling for blocks of variables. Better psychological health status, on a 20-point scale, was associated with lower risk of mortality when adjusted for socio-demographic factors (HR 0.95 per unit increment, 95% CI 0.91–0.99), but not statistically significant after adjustment for other factors.

Comorbid diagnosis of SMI was not significantly associated with mortality in this cohort. However, the presence of comorbid PD or AUD were found to be associated with increased mortality in all models, including the fully adjusted model (adjusted HR 2.15, 95% CI 1.17-3.95, p=0.014; HR 2.28, 95% CI 1.54-3.36, respectively).

In addition, I tested for the presence of interactions between comorbid PD, age and gender (*p*=0.364; *p*=0.641 respectively), and comorbid AUD, age and gender (*p* = 0.052; *p*=0.399 respectively) with all-cause mortality outcome, but none were detected (data not shown in tables).

Table 4.3 Crude and age and gender adjusted Cox regression models for associations with all-cause mortality in individuals with Opiate Use Disorder (OUD).

	Crude Hazard Ratio (95% CI)	Adjusted by Age & Gender	Age & gender Adjusted P Value
Psychiatric Well-Being			
Psychological Health Status*	**0.96 (0.92 - 0.99)**	**0.96 (0.92 - 0.99)**	**0.013**
Comorbid Serious Mental Illness			
Not Present	Referent	Referent	
Present	1.21 (0.70 - 2.09)	1.18 (0.69 - 2.05)	0.544
Comorbid Personality disorder			
Not Present	Referent	Referent	
Present	**1.90 (1.15 - 3.13)**	**2.04 (1.23 - 3.36)**	**0.006**
Comorbid alcohol use disorder			
Not Present	Referent	Referent	
Present	**2.48 (1.83 - 3.37)**	**2.42 (1.77 - 3.28)**	**<0.001**
Socio-Demographic Factors			
Age at first F11 diagnosis**	**1.04 (1.03 - 1.06)**	**1.04 (1.03 - 1.06)**	**<0.001**
Gender			
Female	Referent	Referent	
Male	1.16 (0.83 - 1.62)	1.08 (0.77 - 1.52)	0.643
Ethnicity			
White British	Referent	Referent	
Other White	0.94 (0.60 - 1.47)	0.95 (0.61 - 1.49)	0.820
Black	**0.46 (0.24 - 0.87)**	**0.45 (0.24 - 0.86**	**0.016**
Other and unknown	**0.21 (0.08 - 0.56)**	**0.24 (0.89 - 0.65)**	**0.005**
Level of deprivation**	1.01 (1.00 - 1.03)	1.01 (1.00 - 1.24)	0.178
Relationship Status			
Not in a relationship	Referent	Referent	
In a relationship	0.60 (0.31 - 1.18)	**0.50 (0.25 - 0.99)**	**0.045**
Severity of Drug Use			
Age at first use			
0-14	Referent	Referent	
15-19	1.07 (0.63 - 1.81)	1.09 (0.64 - 1.85)	0.754
20-24	**0.46 (0.24 - 0.88)**	**0.47 (0.25 - 0.90)**	**0.021**
25-29	0.52 (0.26 - 1.06)	0.50 (0.25 - 1.02)	0.106
30+	0.83 (0.46 - 1.52)	0.60 (0.33 - 1.12)	0.106
Frequency of opiate use			

None	Referent	Referent	
1 day - 27 days	**0.62 (0.41 - 0.93)**	0.67 (0.44 - 1.01)	0.056
Everyday	0.77 (0.53 - 1.12)	0.89 (0.61 - 1.31)	0.558
Total Number of Drugs Used**	0.98 (0.88 - 1.08)	0.99 (0.90 - 1.10)	0.862
Risk Behaviours			
Injected			
Not injected	Referent	Referent	
Injected	**1.77 (1.30 - 2.41)**	**1.78 (1.31 - 2.43)**	**<0.001**
Physical Health			
Physical Health Status*	**0.90 (0.87 - 0.93)**	**0.90 (0.87 - 0.93)**	**<0.001**

Statistically significant ($p<0.05$) hazard ratios are in bold.

*Continuous variable, calculated per unit increase in the psychological/physical health status scale. The higher the score for psychological/physical scale, the better the psychological/physical health status.

** Continuous variable, calculated per unit increase in the deprivation score. The higher the score, the higher the level of deprivation/older age at first F11 diagnosis/higher number of total drugs used.

Table 4.4 Cox regression analyses of associations between psychological health and all-cause mortality in individuals with opiate use disorder (OUD).

	HR Adj. for Socio-demographic factors [(a)] (95% CI)	HR Adj. for Age, Gender & Severity of Drug Use [(b)] (95% CI)	HR Adj. for Age, Gender & Risk Behaviours [(c)] (95% CI)	HR Adj. for Age, Gender & Physical Health [(d)] (95% CI)	Fully Adjusted Model [(e)] (95% CI)
Psychological Well-Being					
Psychological Health Status	**0.95 (0.91 - 0.99)**	0.97 (0.93 - 1.00)	0.97 (0.93 - 1.01)	1.02 (0.98 - 1.06)	1.01 (0.97 - 1.06)
Comorbid Serious Mental Illness					
Not Present	Referent	Referent	Referent	Referent	Referent
Present	1.23 (0.70 - 2.18)	0.99 (0.50 - 1.96)	1.14 (0.63 - 2.05)	0.90 (0.46 - 1.77)	0.72 (0.34 - 1.53)
Comorbid Personality disorder					
Not Present	Referent	Referent	Referent	Referent	Referent
Present	**2.04 (1.19 - 3.49)**	**2.01 (1.15 - 3.52)**	**2.10 (1.25 - 3.53)**	**2.33 (1.38 - 3.93)**	**2.15 (1.17 - 3.95)**
Comorbid Alcohol Use disorder					
Not Present	Referent	Referent	Referent	Referent	Referent
Present	**2.38 (1.71 - 3.31)**	**2.47 (1.73 - 3.53)**	**2.42 (1.77 - 3.32)**	**2.24 (1.88 - 3.13)**	**2.28 (1.54 - 3.36)**

(a) Age at OUD diagnosis, Gender, Ethnicity, Level of Deprivation, Relationship status
(b) Age at OUD diagnosis, Gender, Frequency of Opiate Use, Age at First Use, Total number of different drugs used
(c) Age at OUD diagnosis, Gender, Intravenous drug administration
(d) Age at OUD diagnosis, Gender, Physical Health Rating
(e) Adjusted for all variables in Table 3
Statistically significant ($p<0.05$) hazard ratios are in bold.

4.4.4 CAUSE-SPECIFIC MORTALITY IN OPIOID USE DISORDER

I was able to obtain data on recorded underlying cause for 83% of deaths in this cohort (146/176) and these are presented in Table 4.5. Overdose was the most common cause of death (31%). When causes of death were grouped into natural/unnatural causes, the majority of deaths were due to natural causes (61%) with liver disease being the largest natural cause subgroup (23%).

The mean age at death was 43 years, but the difference between mean age at death in patients dying from unnatural and natural causes was almost a decade. AUD and PD were independently associated with increased risk of mortality by liver disease (Table 4.6) (sub-distribution hazard ratio [SHR] 7.28, 95% CI 2.65-19.97; SHR 3.82, 95% CI 1.40-10.46). AUD was also significantly associated with overdose death (SHR 2.53, 95% CI 1.14-5.61).

No significant associations were found for deaths by causes other than the above. Of those who died of alcoholic and other hepatic causes, 65% had previously received an AUD diagnosis on the ePJS system (data not shown in tables).

Table 4.5 Underlying causes of death among opioid dependent individuals.

Underlying cause of death	N (%)	Males (%)	Females (%)	Mean age at death (SD)
Overdose	45 (31)	26 (18)	19 (13)	38 (7.93)
Alcoholic and unspecified liver disease	34 (23)	27 (18)	7 (5)	45 (8.52)
Infectious disease	14 (10)	11 (8)	3 (2)	44 (7.71)
Pneumonia and other pulmonary	18 (12)	14 (10)	4 (3)	49 (8.82)
Other natural causes	23 (16)	16 (11)	7 (5)	49 (11.51)
Other external causes	12 (8)	11 (8)	1 (1)	38 (8.53)
Total underlying causes of death	146	105 (72)	41 (28)	43 (9.85)

Table 4.6 Competing risk regression analyses of factors associated with cause-specific mortality in opioid-dependent individuals in fully adjusted models.

	Fully adj. SHR for overdose mortality (95% CI)*	**Fully adj. SHR for alcoholic and other liver disease mortality (95% CI)***	**Fully adj. SHR for all other causes of mortality (95% CI)***
Psychological Well-Being			
Psychological Health Status	1.02 (0.92 - 1.13)	1.01 (0.93 - 1.10)	1.02 (0.95 - 1.10)
Comorbid Serious Mental Illness			
Not Present	Referent	Referent	Referent
Present	0.75 (0.15 - 3.76)	0.30 (0.05 – 1.97)	0.46 (0.10 – 2.18)
Comorbid Personality disorder			
Not Present	Referent	Referent	Referent
Present	1.34 (0.38 - 4.71)	**3.82 (1.40 – 10.46)**	2.11 (0.68 - 6.53)
Comorbid Alcohol Use disorder			
Not Present	Referent	Referent	Referent
Present	**2.53 (1.14 - 5.61)**	**7.28 (2.65 – 19.97)**	0.89 (0.44 - 1.81)

*Adjusted for socio-demographic factors, severity of drug use, risk behaviours and physical health (see Table 3 for full list of confounders)

Statistically significant ($p<0.05$) sub-distribution hazard ratios (SHR) are in bold.

4.5 DISCUSSION

4.5.1 PRINCIPAL FINDINGS

Analyses presented in this investigation have shown that individuals with OUD have more than four times the risk of mortality compared to the general population. A further two-fold increased risk of all-cause mortality was identified in OUD patients with comorbid PD and AUD, compared to those without these comorbidities. Those with AUD in addition to OUD had twice the risk of fatal overdose and more than seven-fold higher risk of death caused by liver disease. Also, those with comorbid PD were at almost four-fold risk of death of liver disease, compared to OUD patients without PD. However, no associations between mortality and serious mental illness, and psychological status were found.

4.5.2 RESULTS IN RELATION TO PREVIOUS RESEARCH

The association between alcohol and mortality (both overdose and liver disease) fits within the current body of knowledge. Alcohol, the most commonly detected concomitant substance in opioid-related deaths (along with benzodiazepines) (PHE, 2016), potentiates the respiratory depressant effect of heroin and other opioids. Thus, concomitant use of alcohol may well lead to fatality from overdose, due to this interaction (Darke et al., 2000). Alcohol abuse is also strongly associated with methadone-related deaths (NTA, 2007). Chronic HCV is a major cause of liver cirrhosis, as is alcohol misuse (McCartney & Beard, 2010; Menon et al., 2001).

HCV occurs at rates between 40% to 90% in injecting drug users (Limburg, 2004) and the combined effect of HCV and alcohol consumption is deleterious for liver disease (Poynard et

al., 1997). The risk for developing cirrhosis in patients who are HCV-positive and abuse alcohol has been reported to be 147 times higher than HCV-positive patients who abstain (Poynard et al., 1997). Comorbid AUD in OUD patients, therefore, presents particular challenges for clinicians; for example, how best to respond to clients who are under the influence of alcohol when presenting for their medication? There is little research evidence to guide the clinician as to how best to respond to these circumstances (NTA, 2009), and given the heightened mortality rates in this group, more research and guidance is needed.

Current research in PD and OUD reports that screening positively for a borderline personality disorder (BPD) was a risk factor for suicide attempts in heroin-using population (Maloney et al., 2007) and highlights the importance of assessing impulsivity and psychiatric comorbidity when determining risk factors for suicidal behaviour (Maloney et al., 2009).

This study investigated mortality risk beyond suicide. The independent association of comorbid PD, with all-cause and liver-disease mortality might reflect the cumulative influences of a more chaotic lifestyle, such as engagement in risk behaviours, alcohol use, difficulties forming stable relationships, impulsivity, and less treatable addiction. It is possible that either the use of opioids is especially harmful for individuals with PD, or the use of heroin or other opioids might aggravate a pre-existing PD. Alternatively, OUDs and some PDs may be tautological (Rounsaville et al., 1998).

There results presented here should, however, be interpreted with caution. Antisocial Personality Disorder, for example, is a particularly problematic diagnosis for drug users. An illicit opioid user, for instance, will have a high chance of qualifying for the diagnosis due to their illicit drug use, regardless of whether they actually have a PD, creating additional

challenges to the treatment providers. Nonetheless, only a small proportion of dual-diagnosis patients actually receive treatment for both PD and OUD disorders (SAMHSA, 2012). Patients with co-occurring disorders can face challenges accessing treatment, as they may be excluded from mental health services if they admit to a substance abuse problem, and vice versa (SAMHSA, 2012).

I did not find a significant association between mortality and psychological health rating - a reliable measure of indication for problems with anxiety, depressive symptoms and other emotional problems (Marsden et al., 2008). Previous literature focusing on the impact of depression and anxiety in opioid users is also mixed; one study found that higher levels of anxiety have been associated with mortality (Gossop et al., 2002), whereas other found no such association (Arendt et al., 2011).

Although studies have consistently shown that between a quarter and a third of heroin users meet the criteria for a life-time diagnosis of major depression (Darke & Ross, 1997; Dinwiddie et al., 1992), I did not see this in my sample - only 3.5% of the cohort received ICD-10 diagnosis of a depressive disorder. This low proportion of comorbid depressive disorders may result from (a) a tendency to under-diagnose depression in people with OUD perhaps because services focus more on the primary OUD diagnosis and/or diagnoses which are deemed to be more life threatening, (b) mood disorder may improve with effective management of the addiction, and (c) reluctance to make a diagnosis which might lead to prescription of another psychotropic medication.

4.5.3 STRENGTHS OF THIS INVESTIGATION

This study has a number of strengths. SLaM is a large provider of secondary mental healthcare in Europe, with close to 100% monopoly provision to its geographic catchment. I was, thus, able to draw on electronic addictions service clinical records of almost five thousand OUD patients, thereby, potentially providing the statistical power (although not specifically calculated) to simultaneously control for a range of potential confounders. SLaM patient death-tracing is regularly updated and is based on death certificates issued across the UK for both active and non-active SLaM patients. Furthermore, I was able to determine 83% of underlying causes of death for this cohort by linking our SLAM data with external ONS data, which include those derived from coroners' reports.

4.5.4 LIMITATIONS OF THIS INVESTIGATION

The results of this study need to be considered with caution, in light of certain limitations. This is an observational study and residual confounding is possible. Potential confounders included use of a deprivation score rather than a direct measure of socio-economic status. The measure for physical health is a single and self-reported measure, which does not capture all possible physical diseases. It should be noted that mean age at ICD-10-F11 diagnosis was 37.5 years, which does not reflect the "classic-profile" of heroin/opioid addicts who will *first* approach services in their early or mid-20s. This is because our data were limited to diagnosis given within the observation period, therefore may not reflect a true representative of age at *first* OUD diagnosis, which may have been given in treatment episodes prior to the start of my analytical period. I was able to establish causes of mortality based on ONS linked data; however, it was decided not to differentiate between deaths coded as intentional (i.e. suicide) and non-intentional (i.e. accidental) overdoses. Furthermore, SLaM is a secondary service

provider, and the sample would not have included heroin users within the community who are not known to addictions services or who seek help privately. The generalizability of findings is, therefore, to specialist secondary care services. Finally, my indicator for depression and anxiety was based on a subjective psychological health status rating and not a clinical diagnosis. I chose this measure because of the surprisingly low numbers of ICD-10 depression diagnoses in the cohort.

Despite the relatively large cohort, the number of deaths within those with SMI comorbidity was small and important effects might have been missed. Future research should explore these associations further using larger samples. Similarly, the relatively small OUD+PD sample put limits on power for further and more detailed analysis. To aid our understanding of mortality risk in this group, further research should focus on differences in specific personality types, and with a particular focus on directions of casualty (i.e. longitudinal analysis). Furthermore, the inclusion criteria included date of OUD and having seen a clinician at least once during the observation period. Therefore, I was not able to explore associations with mortality by frequency of clinician contact - to establish the possible differences in hazard ratios for people with the minimum criteria for inclusion compared to those with frequent clinician contact during the study timeframe. This, also, is a worthwhile research target.

4.6 CONCLUSION

These findings carry important implications for clinicians, researchers and service providers. The results suggest among people with OUD, a patient group with an already substantially elevated risk of premature mortality, the presence of co-morbid PD and/or AUD puts these individuals at even greater risk. This marked observation should prompt a change of practice for clinicians and also for those responsible for defining and purchasing health care services. Existing treatments for OUD are already known to reduce mortality (Cornish et al., 2010) and the treatment being delivered influences resulting long-term mortality (Faggiano et al., 2003). Correctly tailored treatment is, therefore, even more important when AUD or PD co-exist with the OUD diagnosis. This study highlights the importance of assessment for PD and AUD in OUD patients in order to identify individuals at substantially elevated mortality risk to enable a more personalized approach to their medical care.

CHAPTER 5 ASSESSING MORTALITY RISK IN OPIOID ADDICTION

The contents of this chapter has contributed to the following:

Publication in a peer-reviewed journal:

Bogdanowicz, K. M., Stewart, R. J., Chang, C-K., Downs, J., Khondoker, M. D. M. R., Shetty, H., Strang, J. S. & Hayes, R. D. (2016). Identifying mortality risks in patients with opioid use disorder using brief screening assessment: Secondary mental health clinical records analysis. Drug & Alcohol Dependence, 164: 82-88.

5.1 SUMMARY

Introduction: Risk assessments are widely used but their ability to predict outcomes in OUD treatment remains unclear. Therefore, the aim of this investigation was to explore whether addiction-specific brief risk screening is effective in identifying high mortality risk groups and if subsequent clinical actions following risk assessment impacts on mortality levels.

Aim: To determine if routine brief risk assessments given to OUD patients actually predict all-cause or cause specific mortality. Also, to determine if these risks may be modified by admission to services.

Methods: OUD patients were identified in the SLaM Case Register. Deaths were identified through database linkage to the national mortality dataset. Cox and competing-risk regression were used to model associations between brief risk assessment domains and all-cause and overdose mortality in 4,488 OUD patients, with up-to 6-year follow-up time where 227 deaths were registered. Data were stratified by admission to general mental health services.

Results: All-cause mortality was significantly associated with unsafe injecting (HR 1.53, 95% CI 1.10 - 2.11) and clinically appraised likelihood of accidental overdose (HR 1.48, 95% CI 1.00 - 2.19). Overdose mortality was significantly associated with unsafe injecting (SHR 2.52, 95% CI 1.11 - 5.70) and clinically appraised suicidality (SHR 2.89, 95% CI 1.38 - 6.03). Suicidality was associated with a twofold increase in mortality risk among OUD patients who were not admitted to mental health services within two months of their risk assessment (HR 2.03, 95% CI 1.67 - 3.24).

Conclusions: Addiction-specific brief risk screening can identify OUD patient subgroups at increased risk of all-cause and overdose mortality, including risks related to suicidality, injecting practices and accidental overdose. OUD patients, where suicidality is evident, who are not admitted into services are particularly vulnerable, as suicidality was associated with an increased mortality risk among OUD patients who were not admitted to mental health after their risk assessment.

5.2 INTRODUCTION

5.2.1 EXISTING LITERATURE

People dependent on heroin or other opioids are up to 14 times more likely to die than their peers (Darke & Ross, 2002). Worldwide, an estimated 69,000 people die from opioid overdose (accidental or deliberate) each year (WHO, 2014). In England and Wales, more than 1,200 deaths registered in 2015 involved an opiate drug (ONS, 2016). Assessing and managing risks is a paramount element of care planning and treatment provision to people with drug dependence, particularly in opioid dependence (DOH, 2007). Assessment of risks within the addictions services should be substance misuse specific, prioritizing directly related risks such as overdose, poly-drug use, suicide and/or unsafe injecting practices (NTA, 2006a, 2006b).

The effectiveness of risk assessment tools in predicting mortality in mental healthcare is unclear. Wand and colleagues (2012) reported the inability to conduct a systematic review due to a paucity of studies evaluating the effectiveness of risk assessments; and found little evidence to conclude whether risk assessments are effective in relation to self-harm or suicide reduction. Studies attempting to identify individuals who are more likely to die by suicide have been largely unsuccessful, primarily due to its low prevalence, even within high-risk groups (Harriss & Hawton, 2005; Kapur, 2005). A recent study of people receiving secondary mental healthcare reported that the level of clinically appraised risk of self-neglect (but not suicide or violence) predicted all-cause mortality, but the study did not stratify results by diagnosis or examined cause-specific mortality (Wu et al., 2012).

5.2.2 AIMS AND HYPOTHESES

Given the differences in aetiology, symptoms, care provision and risk factors between mental health diagnostic groups, it is important to investigate these separately as advised by the NTA (NTA, 2006a, 2006b). Therefore, the aim of the investigation presented in this chapter was to determine if addiction-specific brief risk assessment, completed for OUD patients, is effective in highlighting risks of all-cause and overdose mortality; to investigate mortality levels in patients clinically appraised as displaying suicidality, increased likelihood of accidental overdose and unsafe injecting practices; and determine if associations between clinically appraised risks and mortality differs depending on subsequent clinical actions such as admission to secondary mental health services and the type of OST prescribed.

5.3 METHODS

5.3.1 STUDY SETTING

Data for this investigation were derived from the SLaM-based CRIS system described in detail in Chapter 3. Study-specific variables and their completion rates were first explored using the front-end CRIS, and the data extraction plan was developed in accordance with the requirements and advice from the bioinformatics team who then extracted the full data set for these analyses.

5.3.2 INCLUSION CRITERIA

As described in Chapter 3, diagnoses in CRIS are coded in accordance with the 10th edition of the International Classification of Diseases (WHO, 1993). This study cohort comprised SLaM patients who were diagnosed with an ICD-10 F11 primary or secondary OUD between 1st April 2008 to 31st March 2014 (inclusive), and who had at least one item completed on the Brief Risk Scale Assessment-Addictions (BRSA-A) during the observation period. Diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using NLP, for which performance is evaluated in Chapter 3.

5.3.3 MAIN OUTCOME MEASURES

All-cause mortality

The main outcome in this study was all-cause mortality in individuals with primary or secondary diagnosis of OUD, within the period 1st April 2008 to 31st March 2014. Every

death in the UK is reported to the ONS-GRO, which is then conveyed to the NHS Care Records Service and available to all NHS organizations. The majority of deaths are registered with ONS within five days and SLaM mortality updates are performed on a monthly basis. This allowed me to establish deaths within the observation period, for both active and inactive SLaM patients. The full procedure for identifying and confirming SLaM patient deaths has been described in Chapter 3.

Cause-specific mortality

Additionally, 68.7% of all those who died had death certificate information. This information allowed me to establish cause-specific mortality, and more specifically coding for overdose mortality. Fatal overdoses included a combination of both intentional (i.e. suicide) and unintentional (i.e. drug poisoning) overdose deaths, with ICD-10 codes X409-X450, Y120, Y125 and F119 sub-classified as such. The relationship between heroin overdose and suicide is problematic due to ambiguous circumstantial information and unclear intent (Cantor et al, 2001), therefore, for these analyses I grouped suicide by overdose and fatal drug poisonings into one group. The cause of death information is based on a static ONS-CRIS data linkage and is more likely to reflect a proportion of delayed as well as recent occurrences of deaths within the ONS (2011), resulting in the 31% missing causes of death in our cohort (see Chapter 3 for more details).

5.3.4 EXPLANATORY VARIABLES

Exposures of interest

The main exposures of interest in this study were patients' risks of suicidality, likelihood of overdose and injecting practices. These three risk domains were recorded using the BRSA-A (described below) in patients with OUD.

Potential confounders

In addition to the main exposures of interest, a number of other covariates were considered as potential confounders. Patients' risks associated with violence, health, social variables, and service use were also recorded on the BRSA-A. Ethnicity and gender are routinely recorded on SLaM electronic patient records in their designated fields. Age was calculated on the date on which individuals received their first BRSA-A assessment within the observation period. As in the previous chapter, ethnic group classifications were condensed to "White British", "Other White background", "African, Caribbean and other black background", and "Mixed, unknown and other".

Area-level deprivation was established by linking the patient's residential postcode to the UK Census data projected for 2007 in lower super output area units. The full procedure for measuring level of deprivation is described in Chapter 3. Homelessness variable was established by merging information from area-level deprivation and homelessness/unstable housing item on the BRSA-A scale.

Information on patient admissions to a SLaM secondary mental health service in the two-month period after BRSA-A assessment was also extracted. This information included

general admissions to SLaM and information on prescription of opioid substitute treatment (OST) medication (i.e. buprenorphine, methadone, Suboxone [buprenorphine/naloxone]) in the 2-month period after BRSA-A completion. Information extracted included both inpatient and outpatient community service admissions/prescriptions in a 60-day (two months) observation period after the BRSA-A completion.

5.3.5 RISK ASSESSMENT INSTRUMENT

Completion of the BRSA-A is a required procedure for the addictions clinical team on all active cases. This risk measure was developed by SLaM clinicians to encourage identification and formal recording of risk areas specific to substance misuse patients; these are then used in their care planning. The BRSA-A should be completed for each service user at the point of referral, as part of the service user's initial assessment when he or she first comes into contact with SLaM services. The completion of the BRSA-A assists in informing clinical staff whether a full risk screen is then required (SLaM, 2011).

The BRSA-A includes twenty-seven binary items (0=no risk; 1=risk detected). These individual items have been sub-classified into seven risk domains: suicidality, accidental overdose, injecting practices, violence, health, social, and service use. The full list of individual BRSA-A items and their classified risk domains is presented in Table 5.1. For analytical purposes, I collapsed relevant BRSA-A items into three domains according to exposures of interest – suicidality, likelihood of accidental overdose and unsafe injecting practice.

The suicidality domain consisted of suicide attempt history, suicidal ideation, carer concern and major mental illness items. The likelihood of accidental overdose domain consisted of reduced tolerance, recent abstinence, alcohol abuse and poly-substance use. The unsafe injecting domain included previous/current injecting, high risk injecting, and sharing of injecting equipment items.

A score of one was assigned if any item within a given risk domain was scored as present; and a score of zero if all items within that risk domain were scored as absent – this increased power for all-cause and cause-specific overdose investigations. I chose to focus on these three domains as exposures of interest because of their likely relationship with mortality in this patient group (WHO, 2013). Remaining BRSA-A items were included in analyses individually, as potential confounders.

5.3.6 STATISTICAL ANALYSIS

The proportional hazards assumptions were checked using likelihood ratio tests, with no statistically significant interaction between the BRSA-A domains, mortality and time. Cox regression (Cox, 1972) survival analyses were used to model the associations between the suicidality, accidental overdose and unsafe injecting domains (obtained from the first BRSA-A assessment in the observation period) and all-cause mortality.

Competing risk regression was performed to model cause-specific overdose deaths for the same domains. The date of 'at risk' period for each individual patient commenced from the date of their first BRSA-A assessment within the observation period (between 1 April 2008

to 31 March 2014) and ended on the day of their death or the end of observation period, whichever came first.

I also used likelihood ratio tests to examine potential interactions between risk domains and admissions to SLaM services in the two-month period after the assessment was conducted, and between risk domains and the OST prescriptions in the same observation period. Where a significant interaction was found I stratified the data accordingly and re-ran the Cox models with all-cause mortality as the outcome. Kaplan-Meier survival curves were used to visualize results for the stratified analyses. All analyses were conducted using STATA 12, with significance levels set at $p< 0.05$.

5.4 RESULTS

5.4.1 COHORT CHARACTERISTICS

The total number of patients with primary or secondary ICD-10 F11 OUD diagnosis within the six-year period between 1st April 2008 and 31st March 2014 was 5,335 and BRSA-A was completed for 84.1% (n=4,488) of those. There were no significant differences between age (calculated at midpoint observation period for this comparison), gender, ethnicity and mortality in people with and without completed BRSA-A assessments.

There were no individual missing items within the group who had the BRSA-A completed. Therefore, the total number of individuals who met the inclusion criteria and whose data were extracted for analysis was 4,488 (71.8% male; 66.9% "White British"), with 227 registered deaths (detailed in Table 5.1).

Patients contributed a total of 17,805 at-risk person years. Age at risk assessment within our observation period ranged from 15 to 73 years with a mean age of 37.6 (SD=9.07), and with mean age at death of 43.7 (SD=9.15). More than a quarter (27.4%) of our OUD cohort were found to have a comorbid major mental illness. The majority of patients (64.2%) were admitted into SLaM services in the subsequent two months after their risk assessment was carried out. Additionally, crude mortality rates were calculated.

Table 5.1 Cohort characteristics (n=4,488).

Variables	Number of individuals	Number of deaths (% per row)
Total	4,488	227 (5.1)
BRSA-A items and domains		
Suicide		
Suicide attempt history	1,279	91 (7.1)
Suicide ideations	306	13 (4.2)
Carer concern	205	17 (8.3)
Major mental illness	1,225	75 (6.1)
Accidental Overdose		
Reduced tolerance	738	47 (6.4)
Recent abstinence	823	41 (5)
Alcohol abuse	1,220	109 (8.9)
Poly-substance	2,615	155 (5.9)
Injecting		
Previously injecting	1,433	102 (7.1)
Currently injecting	1,047	81 (7.7)
High risk injector	515	49 (9.5)
Share injecting equipment	367	32 (8.7)
Violence		
Violent past	1,051	45 (4.3)
Violent thoughts	84	5 (6)
Violent behaviour	119	8 (6.7)
Violence Concern	117	10 (8.6)
Health BRSA Items		
BBV Infections	900	92 (10.2)
Hist. of substance related seizures	588	59 (10)
Unmet needs	717	92 (12.8)
Cognitive impairment	220	24 (10.9)
High risk sexual behaviour	258	14 (5.4)
Social BRSA Items		
Homeless / unstable housing	1,341	76 (5.7)
Childcare / social service problems	392	17 (4.3)
Social isolation	1,246	88 (7.1)
Self-neglect	816	74 (9.1)
Criminal activity	1,037	47 (4.5)
Service Use Items		

Erratic engagement	880	56 (6.4)
Socio-demographic variables		
Age at assessment		
15-24	358	9 (2.1)
25-29	614	13 (2.1)
30-34	833	36 (4.3)
35-39	888	47 (5.3)
40-44	869	45 (5.2)
45-49	536	33 (6.2)
50+	390	44 (11.3)
Gender		
Males	3,224	166 (5.2)
Females	1,264	61 (4.8)
Ethnicity		
White British	3,002	170 (5.7)
Other White	622	32 (5.1)
Black	466	15 (3.2)
Mixed, unknown & other	398	10 (2.5)
Level of deprivation (in tertiles)		
Low (2.19 -27.42)	1,468	67 (4.6)
Moderate (27.43 - 37.0)	1,470	77 (5.2)
High (37.1+)	1,474	82 (5.6)

5.4.2 ALL-CAUSE MORTALITY FOR BRSA-A RISK CLUSTERS

Crude mortality rates per 10,000 person years (PY) for all-cause and cause-specific mortality are presented in Table 5.2 below. Furthermore, associations between suicidality, accidental overdose and unsafe injecting BRSA-A risk domains and all-cause mortality are represented in Table 5.3. In the fully adjusted models with all-cause mortality as an outcome, BRSA-A assessed unsafe injecting and likelihood of accidental overdose was associated with increased risk of all-cause mortality (HR 1.53, 95% CI 1.10 - 2.11; HR 1.48, 95% CI 1.00-2.19, respectively).

5.4.3 CAUSE-SPECIFIC MORTALITY FOR BRSA-A RISK CLUSTERS

I was also able to obtain data on recorded underlying cause for 68.7% of deaths in this cohort (156 / 227), with overdose deaths (both accidental and intentional) being the largest group (n=44). Other predominant causes of deaths within this cohort were deaths from hepatic causes (n=39) and infectious diseases (n=35) (data not shown in tables). In the fully adjusted competing risk regression models I found that BRSA-A assessed suicidality and unsafe injecting risks were independently and significantly associated with increased overdose mortality (SHR 2.89, 95% CI 1.38 - 6.03; SHR 2.52, 95% CI 1.11 - 5.70, respectively). Likelihood of accidental overdose was not associated with fatal overdose in these analyses.

Table 5.2 Crude mortality rates (CMR) per 10,000 person years (PY) in all-cause and cause-specific mortality in individuals with opioid use disorder

	PY of observation	All-cause mortality		Overdose mortality		Other deaths	
		n deaths	CMR per 10,000 PY	n deaths	CMR per 10,000 PY	n deaths	CMR per 10,000 PY
TOTAL	17,658	227	128.6 (112.5 - 146.3)	44	24.9 (18.1 - 33.4)	112	63.4 (52.3 - 76.3)
Suicide							
No risk	10,405	107	102.8 (84.4 - 124.1)	12	11.5 (6.0 - 20.1)	63	60.5 (46.6 - 77.4)
Risk Detected	7,254	120	165.4 (137.3 - 197.5)	32	44.1 (30.2 - 62.2)	49	67.5 (50.0 - 89.2)
Accidental Overdose							
No Risk	4,111	33	80.3 (55.3 - 112.5)	3	7.3 (1.5 - 21.3)	21	51.1 (31.6 - 78.0)
Risk Detected	13,547	194	143.2 (123.4 - 164.7)	41	30.3 (21.7 - 41.0)	91	67.2 (54.1 - 82.4)
Injecting							
No Risk	8,693	66	75.9 9 (58.8 - 96.5)	11	12.7 (6.3 - 22.6)	33	38.0 (26.1 - 53.3)
Risk Deteted	8,965	161	179.6 9 (153.1 - 209.3)	33	36.8 (25.4 - 51.7)	79	88.1 (70.0 - 109.7)

Table 5.3 Fully adjusted Cox and competing risk regression models examining associations between all-cause and cause-specific mortality and BRSA-A appraised suicidality, likelihood of accidental overdose and unsafe injecting.

Risk Cluster	Fully adj.[a] all-cause HR (95%CI)	p value [a]	Fully adj.[a] SHR for overdose[b] deaths (95% CI)	p value [a]	Fully adj.[a] SHR for deaths other than overdose (95% CI)	p value [a]
Suicidality						
None detected	Reference		Reference		Reference	
Detected (n=1,929, 120 deaths)	1.23 (0.92 - 1.64)	0.154	**2.89 (1.38 - 6.03)**	**0.005**	0.83 (0.55 - 1.26)	0.378
Likelihood of Accidental Overdose						
None detected	Reference		Reference		Reference	
Detected (n=3,416, 194 deaths)	**1.48 (1.00 - 2.19)**	**0.049**	2.82 (0.83 - 9.62)	0.097	1.23 (0.73 - 2.08)	0.43
Unsafe Injecting						
None detected	Reference		Reference		Reference	
Detected (n=2,249, 161 deaths)	**1.53 (1.10 - 2.11)**	**0.011**	**2.52 (1.11 - 5.70)**	**0.027**	1.37 (0.83 - 2.29)	0.221

HR, hazard ratio; CI, confidence interval; SHR, sub-distribution hazard ratio.

a. Adjusted for all variables listed in Table 5.1

b. Accidental and intentional overdoses

Statistically significant ($p<0.05$) hazard ratios are in bold

Table 5.4 Cox regression analyses examining associations between suicide risk domain and all-cause mortality in individuals with opioid use disorder stratified by post BRSA-A admission to SLaM.

	Hazard Ratio (95% CI), P value			
	Crude HR (95% CI)	p value	Fully adjusted[a] HR (95% CI)	p value[a]
Not admitted (N = 1602, 90 Deaths)				
No suicidality detected	Reference		Reference	
Suicidality detected (n=631)	**2.37 (1.56 - 3.62)**	**<0.001**	**2.03 (1.67 - 3.24)**	**0.003**
Admitted (N = 2881, 137 Deaths)				
No suicidality detected	Reference		Reference	
Suicide risk detected (n=1,294)	1.27 (0.91 - 1.78)	0.162	0.91 (0.63 - 1.32)	0.636

HR, hazard ratio; CI, confidence interval.

a. Adjusted for all variables listed in Table 5.1.

Statistically significant ($p<0.05$) hazard ratios are in bold

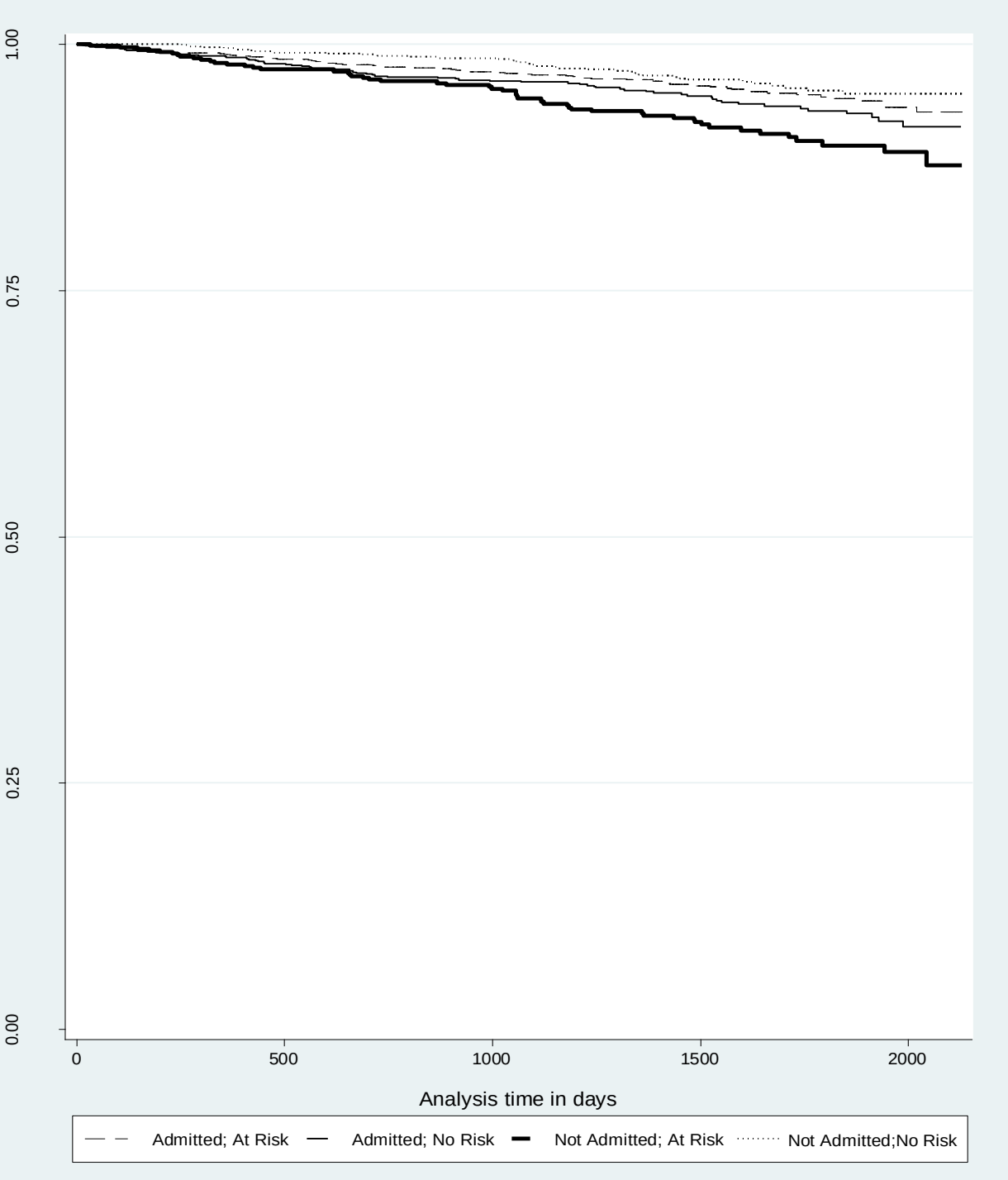
5.4.4 ADMISSIONS TO SERVICES AND BRSA-A RISK ASSESSMENT.

In view of the significant findings above (Table 5.3), I further tested for the presence of interactions between admission in the two-month period immediately after BRSA-A assessment and 1) suicidality, 2) accidental overdose and 3) unsafe injecting domains, in models where the outcome was all-cause mortality. An interaction between BRSA-A suicide risk and SLaM admission was found. Additionally, in all-cause mortality models, I tested for interactions between the types of opioid substitute treatment (i.e. buprenorphine, methadone, Suboxone [buprenorphine/naloxone]) and the three BRSA-A risk domains mentioned above, but none was found (data not in tables).

After stratifying the analysis by admission to SLaM services (presented in Table 5.4) I found that an association between BRSA-A suicidality and all-cause mortality was present in the group who had not been admitted into SLaM services in the two months after their risk assessment (HR 2.03, 95% CI 1.67 - 3.24), but not for the admitted group.

The Kaplan-Meier survival curve in Figure 5.1 visualizes results for suicide risk domain stratified by admission to SLaM service showing the reduced survival in BRSA-A patients where suicidality was assessed as being present who were not admitted. Of all those admitted, 65.9% were admitted to addiction services, with other most common admissions being to psychological medicine and psychosis departments (data not shown in tables).

Figure 5.1 Kaplan-Meier survival curve for BRSA-A suicidality domain and admissions to SLaM services (in days).



5.4.5 ESTABLISHING REASONS FOR NON-ADMISSION

To establish the cause of non-admission, a manual search (where all free-text clinical notes and correspondence were reviewed) in the electronic patient records was conducted in a random sample of 200 patients who were not admitted to services in the 2-month period after their risk assessment (n=100 where suicidality was assessed as being present; n=100 where suicidality was not evident). Of those where suicidality was classified as being present, a manual electronic patient data search revealed that the leading causes for non-admission were loss of contact with the patient (51%) and transfer out of services (26%). Similarly, in the sample where suicidality was not evident, the leading causes for non-admissions were loss of contact with the patient (48%), transfer out of services (22%) and incarceration (11%). No interactions between BRSA-A risks of unsafe injecting and likelihood of accidental overdose and admission to services were found.

5.5 DISCUSSION

5.5.1 PRINCIPAL FINDINGS

Three important findings arising from this study need to be noted. First, addiction-specific brief risk screening assessment may provide useful information to identify subgroups at elevated risk of mortality. Second, specific domains within the BRSA-A were particularly informative - suicidality was found to be associated with increased risk of overdose mortality; unsafe injecting practices were associated with both all-cause and overdose mortality; and increased likelihood of accidental overdose was associated with all-cause mortality but not fatal overdoses. Finally, suicidality was associated with a twofold increased all-cause mortality risk among OUD patients who were not admitted to mental health services within two months of their risk assessment. However, I found no evidence that suicidality presented a similar risk in the subgroup who were admitted into mental health services during this time frame. These finding suggest that OUD patients with clinically evident suicidality who are not admitted to mental health services promptly may be particularly vulnerable.

5.5.2 RESULTS IN RELATION TO PREVIOUS RESEARCH

Whilst the relationship between drug injecting practices and increased all-cause and overdose mortality in OUD is consistent with current literature (Degenhardt et al., 2011; WHO, 2013), the relationship between overdose, suicide and intent is not as clear. Several studies have questioned to what extent heroin overdoses are de facto suicide attempts. An association between heroin overdose and suicide was noted, for example, in a study of 77 overdose survivors admitted to accident and emergency, with 49% reporting suicidal thoughts or

feelings immediately prior to overdose (Neale, 2000). In another study, among a London treatment sample, 50% of those with a history of overdose had two attempted suicides compared to 18% of those with no history of overdose (Vingoe et al., 2009). However, Darke and Ross (2000) reported that while 40% of methadone maintenance participants had attempted suicide, only 10% had done so by means of a deliberate heroin overdose. Drug overdose was the most common method of attempted suicide, but by means of non-opioid pharmaceutical preparations. Conversely, heroin overdose among their participants overwhelmingly appeared to be accidental (92%).

My data suggest that screening positively on at least one item within the suicidality domain (including suicide attempt and/or ideation, carer concern or major mental illness) is, independently of accidental overdose risk factors, associated with an almost three-fold increase in fatal overdose. Although I do not know whether fatal overdoses in this cohort were indeed caused by heroin, other drugs, or a mixture of the two, it is noteworthy that in 2014 in England and Wales, more than a half of all deaths from drug poisoning involved an opiate drug (ONS, 2015).

Second, because the intent was unknown, I do not know which overdose deaths in our cohort were accidental and which were suicides. However, I did find an association between suicidality and overdose fatalities and did not find associations between increased likelihood of accidental overdose and overdose fatalities. This could be interpreted either that most overdose fatalities were deliberate (suicides), or that identification of patients as 'likely to accidentally overdose' resulted in higher visibility to services which then resulted in improved healthcare. Increased likelihood of accidental overdose may be addressed within addiction services, for example, by overdose training or supply of naloxone antidote.

However, suicidality may be much more complex and problematic to address and with the need for dual-diagnostic/multidisciplinary care plan approaches addressing high levels of underlying depression and other psychiatric comorbidities (Bogdanowicz et al., 2015; Cantor et al., 2001; Darke et al., 2007).

The elevated mortality risk in patients where suicidality was evident, and who were not admitted to mental health services in the subsequent two months, highlights the importance of admission, access to services and treatment provision. McCowen and colleagues describe history of admission as being a risk factor for mortality in this patient group (McCowan, Kidd, & Fahey, 2009). However, my study suggests that timing of admission itself is a protective factor for those at risk. Furthermore, non-admission into services was largely due to loss of contact and transfers out of service/catchment area. Drop-out from treatment (and relapse) and erratic engagement in services appears to be highly prominent in this patient group, and both are known to increase mortality considerably (Degenhardt et al., 2011; Zanis & Woody, 1998). Similarly, times of transition between services involved in the care of people with opioid dependence are particularly 'risky', for example after release from prison (Merrall et al., 2010). OUD patients who are assessed as being at risk of suicide and, subsequently, disengage with current services may require more determined strategies for patient follow-up and service transition due to their high risk of mortality. Without better outreach for these poorly engaged groups, current policy will maintain inequalities for more vulnerable groups.

5.5.3 STRENGTHS AND WEAKNESSES OF THIS INVESTIGATION

The results of this study need to be considered in light of certain limitations, alongside acknowledgement of strengths. SLaM is a large provider of secondary mental healthcare in Europe, with close to 100% monopoly provision to its geographic catchment. As a result, I was able to draw on electronic addictions service clinical records of almost five thousand OUD patients allowing to simultaneously control for a range of potential confounders. The inclusion criteria specified primary or secondary OUD diagnosis. Whilst the use of NLP applications allowed me to supplement the existing structured fields, it did not allow to me establish whether these diagnoses were primary or secondary, and measure their impact on outcomes.

SLaM patient death-tracing is regularly updated and is based on death certificates issued across the UK for both active and non-active SLaM patients. This is not the case for underlying cause of death, which derives from additional static ONS linked data. Information on underlying cause of death was only present in 69% of cases. Additionally, as discussed, I could not differentiate between intentional (i.e. suicide-related) and non-intentional (i.e. accidental) overdose deaths. Similarly, toxicology reports were not available, and it was therefore unclear which drugs were involved in the overdose deaths.

The clinical risk assessment information used for analysis was the first within the observation period but may not have been the first risk assessment conducted in an individual's lifetime. Given the mean age of our cohort as 37 years, there will be individuals who have had previous treatment episodes and subsequently previous risk assessment conducted, occurring prior to our observation period. Similarly, I do not know if any (and which) circumstantial/treatment changes occurred in the period beyond the subsequent two months

after their risk screen and until their death/end of observation period, which might have influenced mortality risk in addition to clinically appraised suicide risk. However, given that a high proportion of people did not enter treatment due to loss of contact, it seems that the combination of suicidality and erratic engagement in services increases mortality risk in the longer term.

It is important to note that my analysis investigated admissions to mental health services across SLaM, and not to addictions services only. I chose to broaden my focus because suicide risk in OUD may not necessarily be attended to within the addiction setting in the first instance, especially in cases of psychiatric comorbidity. The identification of reasons for non-admission was extracted from a random sample and not the entire non-admitted sub-cohort. Although the administration of BRSA-A assessments is mandated in practice, only 84% of OUD patients had the BRSA-A scale completed.

Finally, more consideration has to be given to the brief risk assessment screen as a measure of exposure status, which has advantages and disadvantages. The BRSA-A was not formally evaluated as a measurement tool in terms of constructs such as inter-rater or test–retest reliability, or its discriminant validity. However, this is a real-world measure, developed by clinicians and is actively used in daily practice, representing valuable and current real-life scenarios.

5.6 CONCLUSION

Prompt identification of those at risk is key. The current chapter provides evidence that addiction-specific risk assessment may be useful in identifying those whose risk may be elevated in a timely manner. The findings also point out associations between suicidality and overdose mortality in people with opioid dependence, and highlights the importance of admission to mental health services for those where suicidality is evident. Prompt identification and management of those at risk using brief risk assessment may be useful to save time, save costs and most importantly, to save lives.

CHAPTER 6 TREATMENT AND TIMING: ANALYSIS OF CLUSTERING OF OVERDOSE DEATHS IMMEDIATELY AFTER CESSATION OF OPIOID SUBTITUTION TREATMENT AND FOLLOWING TRANSFERS OF PATIENTS AND THEIR CARE

The contents of this chapter have contributed to the following:

Publication in a peer-reviewed journal:

Bogdanowicz, K.M., Stewart, R., Chang, C.K., Shetty, H., Khondoker, M., Day. E., Hayes, R.D., Strang, J. Excess overdose mortality immediately after cessation of opioid substitute therapy and following transfer of patients and their care: findings from analysis of integration of deaths data with catchment area healthcare data on a sample of opioid use disorder patients. *Addiction*. (manuscript submitted)

6.1 SUMMARY

Aims: The aim of the analysis reported in this chapter was to investigate clustering of deaths in the period immediately after transfer of patients and their care and after end of OST, in a cohort of opioid dependent individuals in specialist addiction treatment.

Methods: Mortality data were identified within a sample of 5,445 patients with OUD who had received OST treatment between 1st April 2008 and 31st December 2013. Circumstances and distribution of the 332 deaths identified within the observation window were explored.

Measurements: Mortality incidence rates after the end of treatment/transfer for overdose mortality.

Findings: The study identified higher concentrations of overdose deaths in the first 28 days after a planned end of OST treatment and within 28 days after a transfer of patient between services, even when continuation of OST treatment had been arranged. Of 32 (56%) patients who died of overdose after a planned OST cessation, 18 patients died within 180 days, of whom 5 died in the first 2 weeks and a further 4 died in the reminder of the first month post-termination of OST. Of the 47 individuals who died from overdose after having been transferred between services, 20 (43%) died within 180 days of this transfer, of whom 9 died in the first 2 weeks and a further 5 died in the reminder of the first month post-transfer.

These results translate into an overdose mortality rate of 77.2 per 1000 person-days within 28 days post-OST cessation/transfer, compared with a rate of 1.9 per 1000 person-days for overdoses after the first month of treatment cessation/transfer (rate ratio [RR] = 41.4; 25.1 - 66.1, 95% CI; p <0.0001).

Conclusions: High clustering of fatal overdoses in the early post-OST period was observed. I also found a substantially higher concentration of deaths in the period immediately following transfer of patients to a different treatment care-provider. This excess mortality is pronounced in the first month post-transfer, and especially so in the first fortnight. Further research is urgently required.

6.2 INTRODUCTION

6.2.1 PREVIOUS RESEARCH

Heroin and other opioids contribute disproportionately to drug-related deaths. The use of heroin and other opioids is rare – only 0.1% of responders in the most recent household-based CSEW, compared with cocaine (2.3%) or cannabis (6.7%) (CSEW, 2015). Nevertheless, heroin and other opioids were involved in 53% of all DRDs, and with fatalities reported as involving heroin and/or morphine (heroin breaks down into morphine and hence morphine-positive often means heroin use) having increased by almost two-thirds between 2012 and 2014 (ONS, 2015).

Research has shown consistently that OST is protective against death (Caplehorn, et al., 1996; Faggiano et al., 2003). More recently, it has also been identified that there is a short-lived substantial excess mortality after termination of OST where, in a national primary care cohort, the risk of death has been found to increase eight-fold in the month immediately after the end of OST (Cornish et al., 2010). Several other studies have reported similar findings (Cousins et al., 2016; Davoli et al., 2007; Strang et al., 2003), but none has examined interruptions to continuity of care, such as transfers of patients to alternative service or care-provider.

The present chapter reports findings from preliminary, exploratory analysis 1of mortality patterns amongst patients with opioid use disorder who have received OST treatment within a large secondary mental health service provider (Perera et al., 2015; Stewart et al., 2009). Within this work, I have examined factors associated with clustering of deaths.

6.3 METHODS

6.3.1 STUDY SETTING

SLaM is one of the largest secondary mental healthcare services in Europe, providing addiction services to a catchment population of approximately 1.36 million residents across seven ethnically and socially diverse, high population density boroughs of south-east London (Perera et al., 2015). In 2008, the CRIS system was developed, which accesses patients' electronic health records in a de-identified format, allowing researchers to search and retrieve complete case records for analysis. There are currently more than 280,000 patients represented on the system. CRIS is approved as a dataset for secondary analysis by Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5), and its protocol is described in detail elsewhere (Perera et al., 2016; Stewart et al., 2009).

6.3.2 INCLUSION CRITERIA

The study sample comprised SLaM patients diagnosed with primary or secondary OUD between 1st April 2008 and 31st December 2013 who died within the same observation period. Diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using NLP application for 'diagnosis', which extracts any text strings associated with a diagnosis statement in order to supplement the structured fields. The performance has been explained and evaluated in Chapter 3 and reported elsewhere (Perera et al., 2015).

Every death in the UK is reported to the ONS-GRO, which is then conveyed to the NHS Care Records Service and is available to all NHS organisation; and consequently in CRIS. This

identifies deaths within the observation period, for both current and previous SLaM patients. The full procedure for identifying and confirming SLaM patient deaths has been described by Chang et al (2010) and is detailed in Chapter 3. In addition, a linkage to data specifically derived from death certificates made it possible to establish the recorded underlying cause of each death in those where this information was available.

6.3.3 MEASURES AND CALCULATIONS

In the present chapter, I investigated potential clustering of deaths after a clinically planned termination of OST and after a transfer of patient and their care to another service or care provider, with arrangement for continuation of OST. The main characteristic of interest in this study was the timing of death, specifically overdose deaths, in OUD patients who were prescribed OST treatment. Incidence rates and relative risk were calculated and Kaplan-Meier curves used to visualise the results.

Treatment episodes

Using CRIS, I extracted de-identified individual records on all patients with an OUD who died between 1st April 2008 to 31st December 2013. Searching backwards from each death date, I looked for the start and end dates of the most recent OST treatment episode. This information was primarily derived from treatment care plan notes, with each OST treatment episode starting with the date of the first prescription for substitute opioids relating to most

recent treatment episode and ended with the expiry of their last prescription. The name of the last prescribed OST medication was also noted.

In all cases, a search through discharge notes and free-text fields, including event notes and correspondence, was also conducted manually for validation purposes and to supplement data not available in the structured fields. In order to perform a systematic and consistent manual data extraction and its coding, a set of 'gold-standard' guidelines were developed first which were then rigidly followed and adhered to during the entire manual extraction process. These guidelines included a set of locations Particular attention was given to treatment episodes with a gap of less than 28 days between the end of one episode and the start date of the next. In such cases, examination of event and discharge notes was particularly useful, as it allowed me to establish whether a patient genuinely stopped and restarted their treatment in a four-week period. The 28-day rule was adopted from Cornish and colleagues (2010).

Categorising reasons for end of treatment

Reasons for cessation of OST treatment were extracted from patients' treatment care plans, in discharge notes and other free-text fields. By cross-examining these sources, I categorised reasons for end of treatment into the following: 1). 'Planned end of OST treatment' (patients with a clinically planned discharge following cessation of OST); 2). 'Transfer' (patients who were transferred to another service or care provider who would then take over patients' care, including OST prescribing); 3). 'Dropout' (patients with a clinically unplanned OST cessation, such as non-compliance, failure to attend key-working sessions and/or failure to

collect prescribed OST medications); and 4). 'Died in treatment' (if death occurred during an OST treatment episode). Types of transfer were also noted.

6.4 RESULTS

6.4.1 SAMPLE CHARACTERISTICS

The total number of patients with primary or secondary ICD-10 F11 OUD diagnosis within the observation window was 5,335, with 385 deaths identified in this sample. Of the 385 individuals who died, 53 (14%) were never prescribed OST within SLaM and/or their records contained no information with regard to their treatment history, and were therefore excluded from further analysis. A further 116 (35%) of the remaining 332 patients died whilst still in OST treatment in SLaM and hence were not considered further in this analysis of deaths post-OST treatment and post-transfer.

The remaining sample of 216 deaths are the focus of the analysis reported in this chapter. They comprised 66 patients with a planned termination of OST treatment, 109 who were transferred to another service or care-provider, and 41 who dropped out of OST treatment.

As presented in Table 6.1, most patients were male, with mean age of 45 years at the time of their death. The median duration of patients' last OST treatment episode was just below 8 months (235.5 days, inter-quartile range 52-560 days) and the median interval between end of treatment/transfer and death was almost 1 year (349 days, inter-quartile range 62-800 days). Most destinations for transfers between services were primary care, followed by

independent/third-sector drug treatment providers, transfer to alternative (usually out of area) CDAT services, and to general hospitals.

Table 6.1 Cohort characteristics (n=216).

	N (%)
Total Study Sample	**216**
Males	151 (69.9)
Age	
>= 29	17 (7.9)
30-39	55 (25.5)
40-49	73 (33.8)
50-59	49 (22.7)
60+	22 (10.1)
Planned OST end	66 (30.6)
Drop-Outs	41 (19)
Transfer between services	**109 (50.5)**
Transfer to primary care	42 (38.5)
Transfer to independent/third-party sector	21 (19.3)
Transfer to alternative community drug treatment service	16 (14.7)
Transfer to general hospital	14 (12.8)
Transfer to prison	5 (4.6)
Other transfers	11 (10.9)
Last prescribed medication	
Methadone	179 (82.9)
Buprenorphine	31 (14.3)
Other (diamorphine, Suboxone, morphine)	6 (2.8)
Last treatment episode duration	
One month or less	37 (17.1)
Between one month and six months	59 (27.3)
Between six months and one year	43 (19.9)
More than one year	77 (35.6)

6.4.2 MORTALITY RATES

Under the assumption that the number of patients under treatment remain constant throughout the observation period, there appears to be a higher concentration of all-cause deaths within a month after a planned end of OST treatment and also high concentrations of deaths in the first month after a transfer between services, even when continuation of OST treatment was arranged.

There were 66 individuals who died after a planned termination of OST treatment and 109 who died after a transfer between services. Of the 66 individuals who died after a planned termination of OST treatment, 27 (41%) died within 180 days of treatment cessation, with 12 of those being within the first 28 days and 7 within the first fortnight post-termination. Of the 109 who died after transfer between services, 43 (39%) died within 180 days of this transfer, with 26 dying in the first 28 days and 17 within the first fortnight post-transfer. Similarly, of the 41 who died after having dropped out of treatment, 12 (29%) died within 180 days of this transfer, with 4 of these being within the first fortnight post-drop-out (details not shown in tables).

The primary interest was in deaths caused by a fatal overdose. I was able to ascertain the cause of death in 96% of patients (208 out of 216), summarised in Table 6.2. Overdose fatalities were the most common (49%) followed by liver-related deaths (14%).

To establish whether transfer of care and termination of OST treatment were associated with increased risk of overdose, I restricted further analysis to fatal overdoses only. Of the 103 individuals who died of overdose, 47 were in the post-transfer subgroup and 32 occurred after a planned end of OST, and with high clustering of overdoses occurring in both subgroups.

More specifically, 20 out of 47 (43%) of the post-transfer overdose deaths occurred within 180 days, of which 9 died in the first 2 weeks and a further 5 died in the remainder of the first month. Similarly, 18 out of 32 (56%) of overdose deaths occurred within 180 days of planned OST cessation, of which 5 died in the first 2 weeks and a further 4 died in remainder of the first month. Twenty-four overdoses occurred in the drop-out group, and with five occurring within 180 days but none were recorded within the first fortnight. Figures 6.1 and 6.2 show distribution of overdose deaths within 180 days post-transfer with continuation of OST treatment and post-treatment with planned cessation of OST, respectively.

Combining the three reasons for OST treatment end (transfer, planned discharge and drop-out), the total follow-up -time was 42,716 person-days, with 311 person-days in the group who fatally overdosed in the first 28 days after post-OST cessation/transfer; and with a rate of 77.2 deaths per 1000 person-days compared with a rate of 1.9 deaths per 1000 person-days in the group who died of overdose at a point after the first month of treatment cessation/transfer. The rate ratio comparing the two groups was 41.4 (25.1-66.1 95% CI; p <0.0001). Figures 6.1 shows the survival probabilities for time since the end of treatment/transfer and overdose mortality for total follow-up time. Figure 6.2 displays the survival probabilities for time since end of treatment/transfer and overdose mortality within 180 days after end of treatment, stratified by reasons for end of treatment.

Table 6.2 Underlying causes of death (n=208/216).

Underlying cause of death	Total (%)	Males	Females
Overdose	103 (49.5)	71 (68.9)	32 (31.1)
Liver disease	30 (14.4)	22 (73.3)	8 (26.7)
Infectious disease	12 (5.8)	9 (75)	3 (25)
Pneumonia and other pulmonary	15 (7.2)	11 (73.3)	4 (26.7)
Other natural cause	30 (14.4)	17 (56.7)	13 (43.3)
Other unnatural cause	15 (7.2)	14 (93.3)	1 (6.7)
Unspecified	3 (1.4)	2 (66.7)	1 (33.3)

Figure 6.1 Kaplan Meier survival curves for time since SLaM treatment cessation/transfer (in days) for overdose deaths.

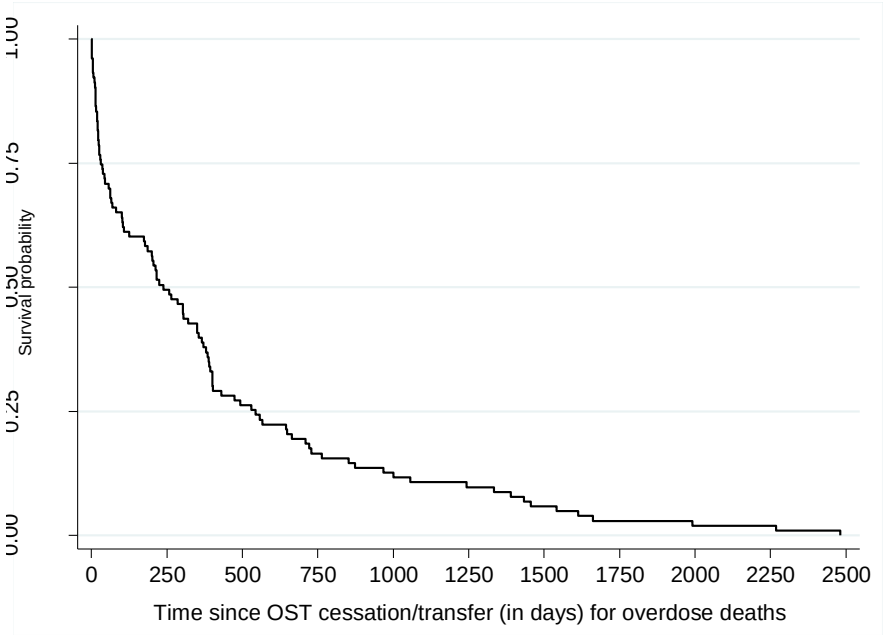
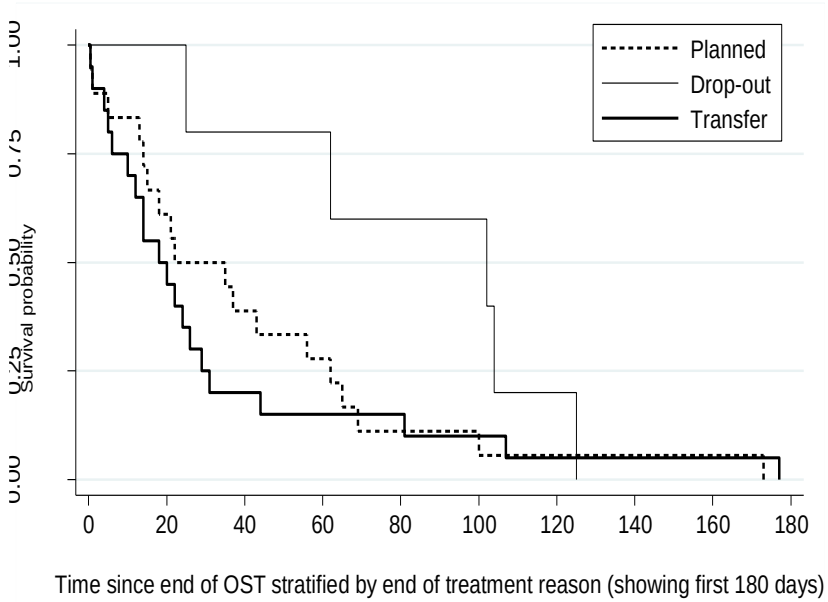


Figure 6.2 Kaplan Meier survival curves for time since SLaM treatment cessation/transfer (in days) for overdose deaths, stratified by reasons for end of treatment or transfer (showing first 180 days).



6.5 DISCUSSION

This study examined circumstances surrounding the deaths of patients with a diagnosis of opioid use disorder who had received OST treatment in SLaM within a near five-year observation period. In addition to substantial clustering of deaths in the early post-OST period as reported by others (Cornish et al., 2010; Cousins et al., 2016; Davoli et al., 2007; Strang et al., 2003), there was also a substantial excess mortality, and especially overdose mortality, in the period immediately following transfer of the patient and their care to a different treatment care-provider, with this excess mortality particularly pronounced in the first month post-transfer.

Increased risk of death immediately after dropout from treatment may not be surprising (Darke et al., 2005) and overdose risk post-termination of OST treatment is already recognised (albeit, limited) (Cornish et al., 2010; Cousins et al., 2016; Davoli et al., 2007; Strang et al., 2003). However, the finding of a marked excess of overdose deaths in the period immediately after transfers of patients and their care despite continuation of OST treatment is new and unexpected. Large 'transferred' subgroups included patients experiencing transitions from secondary to primary care or to large independent (i.e. non-NHS) care-provider organisations who had secured new NHS contracts after the introduction of competitive tendering procedures (DoH, 2013). If the purpose of such re-organisation is to achieve greater effectiveness and more cost-effective use of resources, then it might have been expected that transfer of patients and their treatments would result in better patient stability, and stable or lowered risk of mortality (Darke et al., 2005); however, these analyses instead indicated a high number of fatal overdoses particularity during the first month post-transfer.

These results need deeper and wider exploration, as little is known about the de-stabilisation that may accompany changes to service delivery. The present data did not allow me to ascertain what happened to patients after a transfer. Consequently, I was not able to establish whether any failures had occurred during the period of transition itself, or whether any de-stabilisation occurred after a successful initial transfer to the new care provider.

This study urgently needs fuller exploration and replication. Before any potential explanations are discussed with regard to the mechanisms behind excess deaths post-transfer with continuation of OST, further investigations should focus on exploring these findings using extended data and adjustments for potential confounders, as well as service-user consultations. Although the current analyses were limited to crude associations, these findings provide important insights into practice, the impact of service organisation (including service re-organisational changes) and the associated risks of overdose deaths.

CHAPTER 7 MULTIVARIABLE ANALYSIS OF RISK OF MORTALITY AFTER CESSATION OF OPIOID SUBSTITUTION TREATMENT AND TRANSFERS OF PATIENTS AND THEIR CARE

7.1 SUMMARY

Introduction: There is evidence that opioid misusers have elevated mortality risk after cessation of OST treatment but little is known about de-stabilisation that may occur with changes to service delivery, such as a transfer to alternative service provider, even when OST medication is arranged to continue.

Aim: The aim of the analysis presented in this chapter was to extend the preliminary analysis outlined in Chapter 6, to investigate the associations between all-cause / cause-specific mortality and the three treatment exit types: planned OST cessation, unplanned OST cessation and transfer of patient and their care with arranged continuation of OST, in relation to in opioid dependency; adjusting for potential confounders.

Methods: OUD patients who were enrolled in OST treatment were identified in the SLaM Case Register, within the observation period between 1st April 2008 and 31st January 2016. Deaths were identified through database linkage to the UK Office of National Statistics national mortality dataset. Cox and competing risk regression models were used to investigate the effect of treatment exit type on all-cause and cause-specific mortality (respectively) in patients diagnosed with OUD.

Results: Of 4,316 OUD patients who met the inclusion criteria 380 had died. Overall, being out of treatment (including time after transfer out of SLaM) was associated with a 7-fold increase of overdose mortality (adjusted SHR 7.51, 95% CI 4.73 – 11.90) in the fully

adjusted models, compared to remaining in treatment. The overdose mortality risk in patients who were being transferred out of SLaM with the view to continue OST treatment with alternative care provider was associated with an eightfold (adjusted SHR 8.82, 95% CI 5.35 – 14.56) increased risk of overdose mortality compared to remaining in treatment. Compared to being in treatment, dropping out of treatment and having a planned OST cessation were also associated with an increased overdose mortality (adjusted SHR 5.43, 95% CI 3.15 – 9.39; adjusted SHR 3.18, 95% CI 1.84 – 5.48, respectively).

Conclusions: In addition to elevated mortality risk post drop-out and post planned cessation of OST treatment, elevated overdose mortality risk is associated with transfer to an alternative service provider with the view to continuing OST treatment. These associations persist after adjusting for a broad range of potential confounders. These findings provide important insights into practice, the impact of service organisation (including service re-organisational changes) and the associated risks of overdose death. The results provide groundwork for further research in relation to the transfer of patients and their care.

7.2 INTRODUCTION

Preliminary analysis examining mortality patterns outlined in Chapter 6 showed high clustering of overdose deaths in the period immediately post-discharge with a planned termination of OST, and post-transfer of patient and their care to an alternative service provider where continuation of OST was arranged.

These findings are novel, unexpected, and provide potentially important insights into practice, the impact of service organisation and the associated risks of overdose deaths. They also provided groundwork for urgently needed further research requiring deeper exploration of findings.

Analysis and, subsequently, findings in the previous chapter were limited - inclusive of only those patients who died, therefore without the possibility for multivariable analysis and adjustment for potential confounders. The present chapter extends the investigations of mortality risk after the end of OST or after a transfer out of SLaM, adjusting for a broad range of potential confounders in a cohort of all OUD patients who received OST within SLaM within specified observation period.

7.2.1 EXISTING LITERATURE

Increased mortality after cessation of OST treatment is thought to be influenced by the loss of tolerance during a subsequent relapse to opioid use (Strang et al., 2003). Studies report elevated risk of mortality after discharge from OST treatment, whether planned or

unplanned (Cornish et al., 2010) and in both inpatient and community drug and alcohol services (Davoli et al., 2007; Strang et al., 2003). However, as discussed in Chapter 2, these studies are limited to cohorts which have: small sample sizes (Strang et al., 2003); restrictive inclusion criteria cohorts (Cornish et al., 2010; Strang et al., 2003); limited adjustment of potential confounding (Davoli et al., 2007); or with no information on the underlying causes of death (Cornish et al., 2010). What is more, none of these studies take into consideration the possible impact of disruptions in patient care (as explored in detail in Chapter 2).

Little is known with regards to de-stabilisation that may occur with changes to service delivery even when OST medication is arranged to continue. Periods of transitions from prison back to the community are known to be associated with high overdose risk immediately after release (Singleton et al., 2003) but, as explained in Chapter 2, research on provision of OST medication pre- and post-release through transitional care programmes is inconclusive (Farrell & Marsden, 2008; Merrall et al., 2010). Cornish and colleagues (2010), discussed in the preceding chapter, have investigated mortality risks post planned OST cessation, but patients who were transferred out of treatment to an alternative service provider (approximately 10% per year) were considered lost to follow-up and not investigated further.

Transfers of patients are a common practice; which might occur as part of a successful patient treatment journey where a transfer from secondary to primary care is deemed appropriate by both the patient and the clinician. Alternatively, a transfer of patients might occur irrespectively of the individuals' treatment stage, for example, in instances of

transfers to independent care-provider organisations who had secured new NHS contracts after introduction of competitive tendering procedures (DoH, 2013).

The 2015 State of the Sector report (DrugScope, 2015) found that 44% of drug and alcohol services had been through tendering or contract re-negotiation in the previous year and 49% of all drug and alcohol services are expected to go through one of these processes again during the year ahead. Concerns were expressed that frequent retendering can be destabilizing for both service users and staff, and constitute a diversion of scarce resources away from the delivery of frontline services (ACMD, 2015). The impact, if any, of these re-organization practices on drug and alcohol service users is unclear.

7.2.2 AIMS

There appears to be a transient elevated risk of death in the very early stages of treatment (first 28 days) (Degenhardt et al., 2009), and briefly, following the end of treatment (Chapter 6). These risks require careful assessment and investigations with a particular attention to circumstances surrounding a treatment end and death, which includes any disruptions in treatment, which were not explored in previous studies.

This chapter extends the preliminary findings presented in Chapter 6 by: 1) investigating risks associated with all-cause and cause-specific mortality after a planned and unplanned OST treatment exit, as well as after a transfer of patient and their care to alternative service provider, where OST was arranged to continue, and 2) adjusting for a broad range of potential confounders.

7.3 METHODS

7.3.1 STUDY SETTING

Data for this investigation was derived from the SLaM based CRIS system, which uses EHRs in a de-identified format, allowing researchers to search and retrieve complete case records for analytical purposes. The CRIS tool is described in detail in Chapter 3. The study-specific variables and their completion rates were first located and explored using the front-end CRIS – which allows researchers to explore, search and retrieve data located in structured fields or undertake key word searches within free text using basic Boolean operators only. Second, a full data extraction plan was created and retrieved using CRIS SQL, where the cohort, unlike in Chapter 6, was not restricted to those who died so that a multivariable analysis could be undertaken. Study-specific variables, their location and extraction format are described below.

7.3.2 INCLUSION CRITERIA

The study sample comprised SLaM patients diagnosed with primary or secondary opioid use disorder (discussed in detail in Chapter 3) between 1st April 2008 and 31st January 2016 and who were prescribed one or more of the following opioid substitute therapy drugs: (i) methadone, (ii) buprenorphine; (iii) Suboxone (naloxone/buprenorphine) within the same observation period. Diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using NLP, the performance and evaluation of which is explained briefly below and in detail in Chapter 3.

7.3.3 MAIN OUTCOME MEASURES

The main outcome measure was all-cause mortality derived from the NHS Care Records Service, and cause-specific mortality derived from the ONS based on coroner reports, with a specific interest in overdose mortality. The full procedure for identifying and confirming SLaM patient deaths has been described in Chapter 3. The patient's follow-up ceased either on the date of their death or at the end of the observation period (31st January 2016), whichever occurred first.

7.3.4 EXPLANATORY VARIABLES

Exposures of interest

The main exposure of interest in this investigation was the type of OST treatment exit from SLaM, including planned treatment cessation, unplanned treatment cessation (i.e. drop out) or the transfer of the patient and their care to another service provider with continuation of OST.

I defined patients as being "on treatment" from the date of their first prescribed OST medication within the observation period until the date of their treatment end date, corresponding with the expiry of their last OST medication. The exception to this rule was in instances where patients had a gap of less than 28 days between the end of one treatment episode and the start of the next. In such cases, I defined the patient as being "on treatment" during this gap. I adapted the "28-day rule" from Cornish and colleagues (2010) where it was considered unlikely that a patient would genuinely stop and restart treatment within a

four-week period. Each patient could contribute to more than one treatment episode in analysis, in instances where a patient entered and completed/dropped out/was transferred more than once within the observation period.

Data for all those who died was validated by a manual search through discharge notes and free-text fields, including event notes and correspondence as explained in detail in Chapter 6. The observation period for the current investigation was extended until 31st January 2016 and additional deaths which occurred between the period of 1st January 2014 and 31st January 2016 were manually validated as in the preceding chapter. That is, by examining electronic medical records individually for all additional deaths by searching backwards from the date of death to establish the start and end dates of patients' last OST treatment episode, as well as the reason for treatment cessation or transfer.

The remaining treatment episode start and end dates (i.e. all treatment episodes for those who did not die and for all preceding treatment episodes for those who died) were extracted from treatment plan structured fields using CRIS SQL. Data was also validated on 100 randomly selected treatment episodes. Data validation involved reading through case notes to establish whether treatment start/end dates which were systematically extracted from structured fields through CRIS SQL (and applied to the entire cohort) accurately represented the treatment histories in the free text for this subsample of patients in CRIS.

Potential Confounders

In addition to the main exposure of interest, a number of other covariates were included in these analyses, as potential confounders. Age, calculated at the start of each on-treatment episode (based on date of birth), and gender are routinely recorded in patient records. Area-level deprivation was established by linking the patient's residential postcode to the UK Census data projected for 2007 in lower super output area units (detailed in Chapter 3). Deprivation score was calculated based on postcodes reported closest to the start of each episode, and with coding for homelessness where appropriate. Ethnic group classifications were condensed to "White British", "Other White background", "African, Caribbean and other black background", and "Mixed, unknown and other". Additionally, I also extracted the name of OST medication prescribed at the start of each on-treatment episode and the last prescribed OST medication before off-treatment or transfer episode commenced.

Based on mortality risks identified in Chapter 4, comorbid diagnosis of PD) and AUD, reported ever before or one month after each episode start, were also extracted for inclusion in these analysis. As with OUD diagnosis, psychiatric comorbidity was extracted from structured fields and using NLP for diagnosis reported in free-text fields. The NLP application for diagnosis sought to extract any text strings associated with the statement of diagnosis in question in order to supplement the existing text fields. Its performance has been evaluated in Chapter 3 and elsewhere (Perera et al., 2015; Sultana et al., 2014). The cohort was classified as having a comorbid diagnosis of PD if they had received either a specific personality disorder (ICD-10-F60) or mixed and other PD diagnosis (ICD-10-F61), and comorbid AUD if they had received an ICD-10-F10 diagnosis. Additionally, an indication of alcohol misuse was derived from NDTMS and combined with AUD diagnosis.

Clinically appraised risk of suicidality, accidental overdose and unsafe injecting practices were identified using the BRSA-A scale, as detailed and fully explored in Chapter 5. The suicidality risk domain consisted of suicide attempt history, suicidal ideation, carer concern and major mental illness items on the BRSA-A. Similarly, the likelihood of accidental overdose risk domain consisted of reduced tolerance, recent abstinence, alcohol abuse and poly-substance use. The unsafe injecting risk domain included previous/current injecting, high risk injecting, and sharing of injecting equipment items. A score of one was assigned if any item within a given risk domain was scored as present; or zero if all items within that risk domain were scored as absent.

Problem substances 1, 2, and 3, derived from NDTMS, were used to generate indicators of poly-drug use. Physical and psychological health status - reliable, self-reported measures of physical and psychological health, were also extracted and used as a proxy indicator of physical and psychological health. This measure is part of the TOP scale, which was formally evaluated by Marsden and colleagues (2008) (as discussed in detail in Chapter 4).

7.3.5 STATISTICAL ANALYSIS

Each individual patient's 'at risk' period commenced from the start date of their first on-treatment episode within SLaM within the observation period and ended on the date of exit from SLaM, the date of their death or was censored at the end of the observation period. Each patient could contribute to more than one treatment episode in the analysis in instances

where a patient re-entered treatment again within the observation period, this clustering was taken into account in all the analyses.

I calculated Cox proportional hazards models (1972) to obtain crude, age and gender adjusted and fully adjusted estimates of the relationship between all-cause mortality and exposures of interest including being off treatment, and the off treatment subgroups (planned, unplanned and transfers where continuation of OST was arranged elsewhere). Cox proportional hazards models were further used to produce crude and age/gender adjusted estimates of the relationship between a range of potential confounders and all-cause mortality. Competing risk regression was performed to investigate a fully adjusted association between being off treatment/ off treatment subgroups and overdose mortality; and to determine fully adjusted associations between being off treatment/ off treatment subgroups and non-overdose mortality.

The fully adjusted models controlled for the following variables: age and gender, socio-demographic factors (ethnicity, deprivation level), OST type (methadone, buprenorphine/Suboxone), risk assessment factors (overdose risk, suicidality, injecting practices), physical and mental health factors (psychological health status, physical health status, comorbid diagnosis of PD), and poly-substance use (the reported number of additional illicit substances used, alcohol misuse or dependence). Interaction between mortality, treatment exit and the type of OST medication prescribed were also tested. Proportional hazard assumptions were checked and met using likelihood ratio tests, with no significant interactions between the treatment exit types, all-cause mortality and time. All analysis were carried out using STATA 12, with a significance levels set at $p<0.05$.

7.4 RESULTS

7.4.1 COHORT CHARACTERISTICS

The characteristics of the cohort are presented in Table 7.1. The total number of individuals extracted from CRIS who met the inclusion criteria was 4,316 (72% male; 67% "White British"), with 380 deaths registered within this cohort. Patients contributed a total of 22,159 person years at risk: 13,123 person years on treatment and 9,036 person years off treatment (including time after a transfer). Age at patient's first entry (within the observation period) to SLaM treatment ranged from 14 to 74 with a mean age 38.8 (SD 8.80) – although this may not have been the patient's first approach to addiction services over their lifetime. The mean age at death was 44 years (SD 9.60). 117 patients died while on-treatment and the median length of OST treatment episode was 270 days (range 91-764). There were 989 planned treatment exits, 670 unplanned exits and 1430 transfers during the observation period, and with 92, 60 and 111 deaths within each exit category, respectively.

Table 7.1 Cohort characteristics (n=4,316).

Variables	Number of individuals	Number of deaths (%)
Total patients	4316	380 (9)
Treatment		
On treatment	4316	117 (3)
Planned exits	989	92 (9)
Unplanned exits	670	60 (9)
Transfers	1430	111 (8)
Gender		
Males	3110	282 (9)
Females	1206	98 (8)
Age*		
15 - 24	303	11 (4)
25 - 29	572	23 (4)
30 - 34	764	47 (6)
35 - 39	849	67 (8)
40 - 44	886	80 (9)
45 - 49	518	63 (12)
50+	424	89 (21)
Ethnicity		
White British	2903	309 (11)
Other white	627	40 (6)
Black	396	15 (4)
Mixed and other	390	16 (4)
Deprivation score* (0-100, in tertiles)		
Low	1270	89 (4)
Moderate	1280	143 (11)
High	1585	127 (8)
Homeless	170	19 (11)
Missing	11	2 (18)
Risk assessment		
Overdose risk		
Not detected	910	61 (7)
Detected	3406	319 (9)
Injecting practices		
Not detected	1881	99 (5)
Detected	2435	281 (12)
Suicadality		
Not detected	2121	160 (8)
Detected	2195	220 (10)
Mental and Physical Health		
Physical health status		
Poor	555	97 (17)
Moderate	1196	132 (11)

Good	2410	141 (6)
Missing	155	10 (6)
Psychological status		
Poor	605	83 (14)
Moderate	1289	125 (10)
Good	2269	162 (7)
Missing	155	10 (6)
Comorbid personality disorder		
No	4044	350 (9)
Yes	272	30 (11)
Poly-substance use		
Number of additional drugs used		
1	1695	177 (10)
2	1904	156 (8)
3+	717	47 (7)
Alcohol misuse or dependence		
No	2859	201 (7)
Yes	1457	179 (12)
OST Drug		
Buprenorphine / Suboxone	962	63 (7)
Methadone	3354	317 (9)

7.4.2 ALL-CAUSE MORTALITY

Table 7.2 summarizes findings from crude and age and gender adjusted Cox regression models of factors potentially associated with all-cause mortality in patients with OUD. There were no significant differences between males and females before or after adjustment for age (adjusted HR 0.98, 95% CI 0.78 – 1.23, p=0.862). Those with comorbid PD and alcohol misuse or dependence had elevated mortality after adjustment for age and gender (adjusted HR 1.77, 95% CI 1.21 – 2.59; adjusted HR 2.42, 95% CI 1.96-2.98, respectively). Patients who were prescribed methadone as part of their OST treatment had increased mortality risk (adjusted HR 1.33, 95% CI 1.04 – 1.70) compared to those who were prescribed buprenorphine or Suboxone (after adjusting for age and gender).

Overall, being out of treatment elevated risk of mortality by almost fourfold before and after adjustment for age and gender (adjusted HR 3.79, 95% CI 2.99 – 4.79) (Table 7.2). This mortality ratio persisted even after full adjustment (adjusted HR 3.78, 95% CI 2.92 – 4.89) (Table 7.3).

Of the three exit types, being transferred out of SLaM to alternative service provider with the view to continue their OST treatment elsewhere was most strongly associated with all-cause mortality in crude (HR 6.16, 95% CI 4.67 – 8.13) and age and gender adjusted models (adjusted HR 5.77, 95% CI 4.37 - 7.61) (Table 7.2). This strong association persisted in the fully adjusted models (HR 5.51, 95% CI 4.03 – 7.54) (Table 7.3).

Both planned and unplanned OST cessations (i.e. drop outs) also had elevated mortality in both crude (HR 2.78, 95% CI 2.08 – 3.73; HR 3.40, 95% CI 2.47 – 4.70 respectively) (Table 7.2), and in fully adjusted models (adjusted HR 2.85, 95% CI 2.10– 3.89; adjusted HR 3.62, 95% CI 2.54 – 5.16, respectively) (Table 7.3).

When compared to a planned OST treatment cessation (instead of comparing to being on treatment), being transferred was associated with an almost twofold greater risk of mortality (adjusted HR 1.91, 95% CI .37 – 2.66, $p>0.001$) but there was no evidence that dropping out of treatment was a greater risk for mortality than a planned OST cessation (data not show in tables). In addition, I also tested for the presence of an interaction between the treatment exit types and the type of OST medication prescribed, but none was detected (data not shown).

Table 7.2 Crude and age and gender adjusted Cox regression models for associations between potential risk factors and all-cause mortality (n=4316).

Variable	Crude HR (95% CI)	Crude *p* value	Age & gender adj. HR (95% CI)	Age & gender adj. *p* value
Treatment Factors				
Overall on treatment	1.00		1.00	
Overall off treatment	3.84 (3.04 - 4.86)	<0.001	3.79 (2.99 - 4.79)	<0.001
Treatment exit Type				
On treatment	1.00		1.00	
Planned	2.78 (2.08 - 3.73)	<0.001	2.69 (2.00 - 3.60)	<0.001
Unplanned	3.40 (2.47 - 4.70)	<0.001	3.69 (2.67 - 5.10)	<0.001
Transfer	6.16 (4.67 - 8.13)	<0.001	5.77 (4.37 - 7.61)	<0.001
OST Type:				
Buprenorphine/ Suboxone	1.00		1.00	
Methadone	1.41 (1.10 - 1.79)	0.006	1.33 (1.04 - 1.70)	0.024
Socio-demographic factors				
Gender:				
Female	1.00		1.00	
Male	1.10 (0.87 - 1.38)	0.430	0.98 (0.78 - 1.23)	0.862
Age*	1.06 (1.04 - 1.07)	<0.001	1.06 (1.04 - 1.69)	<0.001
Ethnicity:				
White British	1.00		1.00	
Other White	0.66 (0.48 - 0.92)	0.014	0.71 9 0.51 - 0.98)	0.039
Black	0.34 (0.20 - 0.57)	<0.001	0.31 (0.18 - 0.52)	<0.001
Mixed and other	0.41 (0.25 - 0.68)	<0.001	0.47 (0.29 - 0.79)	0.004
Deprivation score				
Low	1.00		1.00	
Moderate	1.49 (1.15 - 1.92)	0.003	1.46 (1.13 - 1.90)	0.004
High	1.23 (0.94 - 1.62)	0.123	1.18 (0.90 - 1.54)	0.233
Risk Assessment				
Overdose risk				
Not detected	1.00		1.00	
Detected	1.56 (1.18 - 2.10)	0.002	1.70 (1.29 - 2.24)	<0.001
Injecting practices				

Not detected	1.00		1.00	
Detected	2.28 (1.82 - 2.87)	<0.001	2.16 (1.72 - 2.71)	<0.001
Suicidality				
Not detected	1.00		1.00	
Detected	1.67 (1.36 - 2.05)	<0.001	1.71 (1.39 - 2.10)	<0.001
Mental and Physical Health				
Physical health status				
Poor	1.00		1.00	
Moderate	0.63 (0.49 - 0.80)	<0.001	0.68 (0.53 - 0.86)	<0.001
Good	0.38 (0.29 - 0.49)	<0.001	0.43 (0.33 - 0.56)	<0.001
Psychological status				
Poor	1.00		1.00	
Moderate	0.73 (0.57 - 0.93)	0.011	0.73 (0.57 - 0.93)	0.011
Good	0.64 (0.50 - 0.83)	0.001	0.64 (0.50 - 0.83)	0.001
Comordid PD				
No	1.00		1.00	
Yes	1.77 (1.21 - 2.59)	0.003	1.77 (1.21 - 2.59)	0.003
Poly-substance use				
Number of additional drugs used*	1.19 (1.03 - 1.38)	0.017	1.20 (1.04 - 1.39)	0.015
Alcohol misuse or AUD				
No	1.00		1.00	
Yes	2.58 (2.09 - 3.16)	<0.001	2.42 (1.96 - 2.98)	<0.001

* Continuous variable, calculated per unit increase. The higher the score, the older the age/number of poly-drug use

7.4.3 OVERDOSE MORTALITY

I was able to obtain data on recorded underlying cause for 73% of deaths in the cohort (277 / 380). Overall, there were 149 fatal overdoses and these include both accidental and intentional poisonings. Liver disease was the cause of death for 44 patients. Other predominant causes were those due to infectious diseases (n=22), pulmonary disease (n=19) and other natural causes (n=27).

In the fully adjusted competing risk models, being out of treatment was associated with a more than sevenfold increased overdose mortality risk compared to being in treatment (adjusted SHR 7.51, 95% CI 4.73 – 11.90). Moreover, compared to being in treatment, overdose mortality was almost nine-fold higher post-transfer (adjusted SHR 8.82, 95% CI 5.35 – 14.56) and more than fivefold higher after dropping out of treatment (adjusted SHR 5.43, 95% CI 3.15 – 9.39).

Additionally, by changing the reference point, I tested whether the planned/unplanned/transferred sub-groups differed from each other. Groups were different in both all-cause mortality (HR 1.52, 95% CI 1.07 – 2.16 transferred vs planned; HR 1.93, 95% CI 1.41 – 2.64 transferred vs unplanned) and overdose mortality (HR 2.78, 95% CI 1.65 – 4.68 transferred vs unplanned; HR 1.42, 95% CI 1.04 – 2.68 transferred vs planned) (data not shown in tables).

Table 7.3 Fully adjusted Cox and competing risk regression examining associations between all-cause and cause-specific mortality and treatment exit types in OUD secondary mental health patients.

Treatment Factors	Overdose deaths (%)	Fully adj.* all-cause HR (95% CI)	Fully adj.* all-cause *p* value	Fully adj.* SHR[1] for overdose[2] deaths (95% CI)	Fully adj.* for OD[±] deaths *p* value	Fully adj.* SHR[1] for deaths other than OD (95% CI)	Fully adj.* other deaths *p* value
Overall on treatment	34 (12)	1.00		1.00		1.00	
Overall off treatment	115 (42)	3.78 (2.92 - 4.89)	<0.001	7.51 (4.73 -11.90)	<0.001	2.01 (1.30 - 3.11)	0.002
Treatment Exit Type							
On treatment	34 (12)	1.00		1.00		1.00	
Planned	31 (11)	2.85 (2.10 - 3.89)	<0.001	3.18 (1.84 - 5.48)	<0.001	2.85 (1.71 - 4.75)	<0.001
Unplanned	29 (10)	3.62 (2.54 - 5.16)	<0.001	5.43 (3.15 - 9.39)	<0.001	2.82 (1.42 - 5.62)	0.003
Transfers	55 (20)	5.51 (4.03 - 7.54)	<0.001	8.82 (5.35 -14.56)	<0.001	2.87 (1.53 - 5.38)	0.001

* Adjusted for all variables listed in Table 1.
[1] Subdistribution hazard ratio
[2] Accidental and intentional overdoses.
[±] Overdose (OD)

7.5 DISCUSSION

7.5.1 PRINCIPAL FINDINGS

Important findings arise from these analyses. First, compared to being enrolled in OST treatment in SLaM, being out of OST treatment (including being transferred out of treatment with the view to continue OST) was associated with a substantially higher risk of mortality. This is especially evident for overdose mortality, which was sevenfold higher out of treatment and eightfold greater when care was transferred to an alternative service provider. Both a planned OST cessation and dropping out of treatment were also associated with elevated risk of all-cause and overdose mortality.

7.5.2 RESULTS IN RELATION TO PREVIOUS RESEARCH

The overall higher risk of death out of treatment for patients with OUD is consistent with existing literature (Brugal et al., 2005; Darke et al., 2005). In particular, dropout from drug and alcohol treatment is known to have markedly increased mortality risk, especially for fatal overdose (Bargagli et al., 2007). The increased risk of death post-planned OST treatment cessation has also been recognised, especially in the first month after cessation of treatment (Cornish et al., 2010; Davoli et al., 2007; Strang et al., 2003). However, this study found more than eightfold excess overdose mortality following the transfer of patient and their care to an alternative treatment care-provider, where the patients' OST was arranged to continue. The finding of a marked excess of overdose deaths following a transfer has not been reported previously.

Changes within treatment, such as a transfer from methadone to buprenorphine are common and are known to be destabilizing for the patient (Breen et al., 2003; Walsh et al., 1994, 1995). Thus, extra care is taken during such periods; and decisions between such transfers are made collaboratively by patients and service providers. Little is known, however, about the de-stabilisation that may accompany changes to service delivery. Transfers of patients are a common practice; Cornish and colleagues (2010) report that around 10% of patients per year are transferred between the services, but this subgroup was excluded from their analysis.

Another large-scale study investigating mortality risk post-treatment cessation does not report on patients who might have been transferred out of treatment (Davoli et al., 2007). A Norwegian study (Ravndal & Amundsen, 2010) of mortality among drug users after discharge from inpatient treatment reports an elevated risk of dying from overdose within the first 4 weeks of leaving medication-free inpatient programmes. The definition of leaving treatment in this study however, involved a completion of inpatient treatment and a transfer to psychosocial rehabilitation. The study reports unadjusted excess overdose mortality rare ratio of 15.7 but all deaths occurred in patients who have dropped out of treatment. Similarly, periods of transitions from prison back to the community are known to have high transient overdose risk after release, but research on provision of OST medication pre- and post-release through transitional care programmes is inconclusive (Merrall et al., 2010; Farrell & Marsden, 2008; Bird et al., 2015).

As described in the previous chapter, transfers might occur as part of a successful patient treatment journey where a transfer from secondary to primary care is deemed appropriate by both the patient and the clinician. Alternatively, a transfer of patients might occur irrespectively of the individuals' treatment stage, for example, in instances of transfers to independent care-

provider organisations who had secured new NHS contracts after introduction of competitive tendering procedures (DoH, 2013) or from prison back to the community.

In the previous investigation (Chapter 6) I found that large 'transferred' subgroups included patients experiencing transitions from secondary to primary care or to large independent care-provider organisations who had secured new NHS contracts after the introduction of competitive tendering procedures (DoH, 2013). Re-organisational changes are thought to be conducted for greater effectiveness and cost-effectiveness. Therefore, one might expect to find successful transfer of patients and their treatments, patient stability, and stable or lowered risk of mortality (Darke et al., 2005), however these analyses instead indicated a high number of fatal overdoses in such groups.

7.5.3 STUDY STRENGTHS

The study has a number of strengths. As discussed in the previous chapters, SLaM is a large provider of secondary mental healthcare in Europe, with close to 100% monopoly provision to its multicultural and ethically diverse geographic catchment. I was thus able to draw on electronic addiction service clinical records of almost five thousand OUD patients allowing adjustment (although not formally calculated) for a broad range of confounders. SLaM patient death tracing is regularly updated and is based on death certificates issued across the UK for both active and non-active SLaM patients. Furthermore, I was able to determine 73% of underlying causes of death for this cohort by linking SLaM data with external ONS data.

7.5.4 STUDY LIMITATIONS

The results of the study need to be considered in light of certain limitations. This is an observational study and residual confounding is possible. Potential confounders included deprivation score rather than a direct measure to socio-economic status. Certain variables, such as HCV status and education level were excluded from analysis due to large number of missing values. SLaM is limited to secondary mental health care patients, therefore does not include patients in primary care or those seeking help privately Opioid addiction is, however, primarily treated within secondary mental health community setting (NDTMS, 2013), and this population would not be captured by other studies restricted to primary care data (e.g. Cornish et al., 2010).

The present data did not allow me to ascertain what happened to patients after a transfer. Consequently, I was not able to establish whether any failures had occurred during the period of transition itself (drop outs), or whether any de-stabilisation occurred after a successful transition to the new care provider. Although I was able to detect high mortality rates associated with being transferred out of treatment and cessation OST treatment, comparisons of immediate risk periods in and out of treatment (i.e. within the first month post-treatment/transfer) was beyond the current scope of this analysis. However, the preceding chapter, which examined circumstances surrounding the deaths of these patients, indicates that this risk may be most prominent in the first month after cessation of treatment and transfer of patient and their care. Additionally, I was unable to measure the potential 'epoch' effect of heroin drought in 2010/11 (SOCA, 2011, 2012, 2013, 2014), whereby background overdose risk may have been lower during earlier in-treatment period of observation and higher during the later off-treatment period of observation.

No formal power calculation was performed in this thesis and it is possible that possible that some analyses were somewhat under-powered, as indicated by large confidence intervals. Finally, the current data could not differentiate between intentional and unintentional overdose deaths. Similarly, toxicology reports were not available, and it was therefore unclear which drugs were involved in overdose deaths.

7.6 CONCLUSIONS

The results presented here, together with those presented in the preceding chapter need fuller exploration and replication. In addition to elevated mortality risk post dropout and post planned cessation of OST treatment, being transferred to an alternative service provider with the view to continue OST treatment was associated with an eightfold increased mortality risk compared to continuing treatment in SLaM. Further investigations should focus on exploring these findings to determine whether deaths following a transfer occur during the period of transition itself (i.e. resulting in drop out), or whether any de-stabilisation occurred after a successful transition and successful continuation of OST. Studies should also focus on determining the exact high-risk periods and establish whether similar transient risk period exists as that identified post OST cessation or post-prison release. These findings provide important insights into practice, the impact of service organisation (including service re-organisational changes) and the associated risks of overdose death and further research is urgently required.

CHAPTER 8 DISCUSSION AND CONCLUSIONS

8.1 SUMMARY OF FINDINGS

Enrollment in treatment is the single most effective road to recovery and to minimize harms associated with opiate drug-use during this journey (Darke et al., 2000; Davidson et al., 2003; McGregor et al., 1998; Pierce et al., 2016). However, certain mortality risks within OUD treatment exist and these need careful exploration and interpretation.

This thesis utilized anonymized patient health records from one of the largest mental health service providers in Europe and explored mortality risk factors, at both patient-level and service-level, in individuals with OUD enrolled in secondary drug and alcohol treatment. The aims of the thesis were:

5. To explore associations between psychological wellbeing, comorbid diagnosis of PD, SMI and AUD, in relation to all-cause and cause-specific mortality in opioid dependence.
6. To determine if addiction-specific, routine brief risk assessments given to OUD patients can predict all-cause or cause specific mortality. Also, to determine if these risks may be modified by admission to services.
7. To investigate clustering of deaths, especially fatal overdoses, in the period immediately after transfer of patients and their care, and after end of OST in a cohort of opioid dependent individuals in specialist addiction treatment.
8. To investigate the associations between planned OST cessation, unplanned OST cessation and transfer of patient and their care with arranged continuation of OST, in relation to all-cause and cause-specific mortality in opioid dependence with adjustment for potential confounders.

In summary, the findings of this thesis provide evidence of the burden of opioid use disorder in secondary mental health services and the general population.

First, this thesis identified that addiction-specific brief risk screening can identify OUD patient subgroups at increased risk of all-cause and overdose mortality. These subgroups include those at risk of accidental overdose, at risk due to injecting practices and at risk of suicidality. Second, the results highlight the need for admission to services, where suicidality is evident, as results in Chapter 4 show reduced survival in patients where suicidality was assessed as being present, but who were not admitted into services following the assessment.

Third, the study found that the presence of co-morbid PD and AUD puts OUD individuals at greater risk of mortality, compared with OUD patients without such co-morbidities. This is true for all-cause mortality, fatal overdose and liver-related fatalities (as seen in Chapter 4).

Finally, investigations of time and context were also conducted. The risk of overdose mortality increased to eightfold in patients whose care was transferred to an alternative service provider where their OST was arranged to continue (Chapter 7) compared to those who remained with their original treatment provider. Mortality was also significantly elevated for patients with a planned OST cessation and in those who have dropped out of treatment, but not to the same extent as those who were transferred (Chapter 7). This is a novel and potentially important finding.

Upon examination of circumstances surrounding the deaths of patients who had received OST treatment it was found that, in addition to substantial clustering of deaths in the early post-OST period, there was also a substantial excess overdose mortality in the period immediately following transfer of the patient and their care to a different treatment care-provider, with this excess mortality pronounced in the first month post-transfer (Chapter 6).

8.2 OPIOID USE DISORDER AND MORTALITY

In England and Wales, deaths involving opioids doubled in the last three years and are now the highest since records began (ONS, 2016). New estimations are therefore required, and evidence from Chapters 4 provides support for the argument that there is a need to focus on deaths by natural causes as well as drug-related deaths.

Cohort studies provide a valuable means of estimating drug related mortality rates. In this thesis, mortality rates amongst the OUD cohort, known to secondary addictions services, was substantially higher than the general population. This is especially elevated for women where the rate was over five times the general population (see Chapter 4). These findings are consistent with existing literature (Degenhardt et al., 2009; Hayes et al., 2011).

While overdose is a major cause of premature mortality amongst heroin using populations, equal consideration should be given to other prominent causes of deaths, especially by natural causes, as seen in Chapter 4. Looking beyond unnatural causes of mortality may help improve our understanding of the pathways to premature mortality among opioid users, identify subgroups at substantially elevated mortality risk and inform commissioning bodies of the extent of services needed for a successful recovery.

Throughout this thesis, overdose deaths constituted the largest proportion of underlying causes of death. Both fatal and non-fatal overdose investigations are certainly a matter of importance. However, the second most prominent cause was attributed to natural deaths, such as liver disease (see Chapters 4-7). This is especially evident in those who misuse alcohol and/or those with PD. These findings are consistent with previous reports, although there

seems to be a limited interest in studying specific risks associated mortality in heroin using populations beyond overdose (Johnson et al., 2015).

8.3 INDIVIDUAL FACTORS AND MORTALITY

The needs of a typical opioid dependent patient are complex and extensive, not only through their level of physical and psychological dependence to the opioid drug but also through poor psychosocial functioning (Arendt et al., 2011; Bargagli et al., 2006; Darke, 2011; Darke & Ross 2002; Ghodse et al., 1985; Gossop et al., 2002; Davoli et al., 1993; Shah et al., 2008). For many people, addiction to opioids is a persistent and relapsing disorder, with only a minority successfully achieving lasting recovery following a single episode of treatment (Dennis et al., 2005; Strang et al., 2014).

Deaths among opioid users predominantly occur among white, long-term, dependent, socially isolated males, especially those who inject drug; with prison histories, who are typically unemployed (see Tables 2.1.-2.2. in Chapter 2). Findings in this thesis are consistent with this view in terms of age, ethnicity, lower socioeconomic status (measured by deprivation score) and injecting practices (Chapter 4, 5 and 7).

Upon review of the literature in Chapter 2, it was found that the impact of psychiatric comorbidity on mortality risk in substance use disorders has received only moderate attention, with existing investigations reporting mixed results (Arendt et al., 2011; Davoli et al., 1993; Gossop et al., 2002; Mattisson et al., 2011) and that in-depth investigations of risks in relation to natural causes of mortality are limited. Both limitations are addressed in this thesis, particularly in Chapter 4.

First, co-morbid physical health problems are often overlooked, despite known elevated rates of cardiovascular and renal disease and diabetes among these populations (Strang et al., 2014; Wadland & Ferenchick, 2004). In this thesis, fatalities due to liver disease (other than those

related to HCV) were extremely common in this patient group (as demonstrated in Chapters 4 - 7). Chapter 4 presented a sevenfold increase in liver-related deaths in OUD patients who misuse alcohol; and, perhaps more surprisingly, a near fourfold risk of liver-related death in OUD patients with a PD, compared to patients without these comorbid problems (in addition to elevated overdose risk in OUD+AUD subgroup). This increase in deaths is thought to be influenced by higher levels of impulsivity and risk-taking behavior – a core feature of a personality disorder (WHO, 1993), which might result in more chaotic lifestyle in addition to that associated with drug use.

Co-morbid psychiatric problems and alcohol misuse in OUD patients are troublesome; and only a small proportion of dual-diagnosis patients actually receive treatment for both PD and OUD disorders (SAMHSA, 2012). Patients with co-occurring disorders can face challenges accessing treatment, as they may be excluded from mental health services if they admit to a substance abuse problem, and vice versa (SAMHSA, 2012). Similarly, opioid patients with a co-occurring alcohol problem, who present themselves to CDAT services might be turned away from receiving their OST medication due to existing risks of concurrent use of opioids and alcohol.

8.4 SERVICE PROVISION AND MORTALITY

The results presented in this thesis add to the current body of knowledge with regards to risks associated with service provision in opioid dependency. They also provide evidence for the need to restructure and/or improve certain aspects of drug and alcohol treatment in the UK. These include the need for effective dual-diagnosis services (Chapters 3-4), better outreach for people with history of erratic service engagement (Chapters 4-6), continuation of care and overdose prevention for those newly discharged and those transferred between services (Chapters 5-6).

This is the first study evaluating the effectiveness of the BRSA-A scale – a "real-world" measure of associated risks, used presently in a large addictions service. We now know that the assessment of drug-related risks, especially accidental overdose, suicidality and those associated with injection of opioids, can be done effectively (Chapter 5) by using a simple, and relatively quick to conduct, assessment. Consisting of only binary items, such a simple scale might be straightforward (but useful) to implement in other services, for better identification of drug-related risks. This would be especially relevant in general medicine or dual-diagnosis OUD patients who present for treatment at services other than addiction services.

Second, Hickman and colleagues (2016) recently highlighted the need to accumulate evidence on risk of mortality on and off OST. They advised that more studies of this kind are needed so that 'stratified medicine' for treatment of OUD can be provided; and that pooled experience and evidence from different health-care systems is necessary in order to tailor specific treatments and ensure that 'the right patient gets the right treatment at the right time'. This thesis addresses this request by investigating mortality after planned and unplanned OST

cessations with the inclusion of transfers between services. Results presented here extend the studies of others (Cornish et al., 2010; Cousins et al., 2016; Davoli et al., 2007; Strang et al., 2003) to identify specific times and locations of increased risk of fatal outcomes.

There is a localization of deaths in time and context. In the "transit zone" between time in prison and post-release return to the community, a large concentration of deaths, occurring particularly during the first fortnight post-release was found (Singleton et al., 2003). Similar clustering at the end of in-patient and post- detoxification from OST has been reported by others (Cornish et al., 2010; Ravndal & Amundsen, 2010; Strang et al., 2003) and in this thesis (Chapters 6-7). The present thesis extends existing literature not only to include data from secondary care and specific causes of death, but also with regards to the transfer of patients during an active enrollment in OST.

No previous study has investigated the impact of transfers of OUD patients and their care (as explained in Chapter 2). These transfers include those from secondary to primary care, which may be deemed as a positive transfer, agreed by both the patient and the clinician. They also include transfers irrespectively of the individuals' treatment stage - for example, in instances of transfers to independent care-provider organisations who had secured new NHS contracts after introduction of competitive tendering procedures (DoH, 2013). Approximately 50% of addiction services are expected to go through such tendering procedures in the new year (DrugScope, 2015). Therefore, more transfers of patients might be expected, potentially resulting in a high number of fatal overdoses.

Greater awareness of times and situations of overdose risk in relation to treatment and subsequent exits from treatment were identified in this thesis. However, strategies to prevent

opiate overdose deaths have been only minimally explored in literature (Strang, 2015). Unless progress is made, the large excess mortality will continue unchecked (Strang, 2015). With this improved understanding of the risk factors in time and context, further research (as will be discussed later) should focus on utilizing these findings to implement effective strategies to prevent fatalities.

8.5 STRENGTHS AND LIMITATIONS

8.5.1 ORIGINALITY

This thesis adds to the existing body of research on risks associated with mortality in heroin using population. This thesis not only addresses patient-level factors but also investigates mortality in relation to service provision and organisational changes – an area with very limited existing literature. No previous studies have evaluated the effectiveness of the BRSA-A in highlighting those OUD patients at highest risk. This thesis also provides evidence for the need for prompt admission to services where suicidality is evident; the need for effective assessment and management of dual-diagnostic patients with PD and alcohol misuse; and highlighted the elevated mortality, especially overdose, associated with discharge from treatment and disruptions in patient care. This thesis also utilises recent technological advantages by using a large anonymised electronic patient records data and externally linked data, and with innovative data extraction approaches. The combination of these provided near-complete patient health records data for robust analysis and adjustment for a broad range of potential confounding factors, which is often limited in existing literature.

8.5.2 DATA SOURCE, STUDY DESIGN AND SAMPLE

This thesis incorporates a series of cohort studies, which has important advantages. Participant-derived recall bias is less likely to occur, as symptoms and treatment progress are recorded by the clinician at or close to the time of their occurrence. The majority of variables used in this thesis did not rely on information recalled from the past (with the exception of age at first drug use, which was used as a potential confounder). However, all measurements are potentially subject to error. Misclassification might occur, as records may be missing or

incomplete. For example, completion of tobacco use information was poor and the variable was removed from analysis (thereby potentially introducing residual confounding, discussed further below).

SLaM is a secondary mental health service therefore generalizability of findings are to those known to secondary mental health services, thereby under-represent users not in touch with services, from whom adverse outcomes might be subsequently more prevalent. Nonetheless, SLaM holds close to 100% monopoly provision to its ethnically diverse and multicultural geographical catchment, hence representative of those seeking secondary care in this catchment.

In January 2017, the CRIS database (which strengths and limitations are described in detail in Chapter 3) held complete ePJS records for more than 280,000 individuals. This figure represents a near 100% representation of the SLaM service-user population, with just 3 patients opting-out of CRIS (which means that their EHRs were not present in CRIS for research purposes) since it was developed. Thus, any potential bias that comes with low response rates was not an issue in this thesis. I was able to draw on electronic addictions service clinical records of approximately 5,000 OUD patients, and with a generous follow-up period of up to 7 years, which increased the likelihood to detect rarer events and longer-term outcomes.

Death tracing is regularly updated (monthly) in SLaM and is based on death certificates issued across the UK for both active and non-active SLaM patients (as described in detail in Chapter 3). Thus, misclassification of mortality was unlikely (unless patient died abroad).

Additionally, I was able to determine the underlying causes of deaths for the majority of deaths in each analysis (83% in Chapter 4; 69% in Chapter 5; 96% in Chapter 6; 73% in Chapter 7). High completion rates for underlying causes of death were important, as lack of this information would result in large number of deaths dropped from analysis, thus potentially introducing selection bias for those with and without specified causes.

It was possible to determine underlying causes of death through data linkage with the ONS data. The completion rates for cause-specific mortality figures differ as the observation periods and the inclusion criteria changed with specific research aims. Furthermore, unlike death-tracing, the cause of death data is a static data linkage, with irregular updates. Each update request requires a number of administrative tasks from both the SLaM linkage team and the ONS team, resulting in severe delays. ONS also reports approximate 6-month to 1 year delay in establishing causes of death (ONS, 2011), which requires analytical period adjustments at extraction-level to avoid having excessive missing data from the most recent deaths in the dataset used for analysis. Furthermore, there is likely to have been differential ascertainment of cause of death by type due to registration delay following referral for coronial investigation of suicide /fatal overdose but probably not for disease causes. Thus, more of the overdoses and suicides than disease deaths are likely to have been missing, with implications for the proportion of deaths assigned to these. I was also unable to determine whether overdoses were deliberate or unintentional as these were grouped together.

Data linkages, while increasing the richness of available data can also present their own set of challenges. Performing new data linkages is a long and complex process. While the current thesis primarily focussed on fatal overdoses, non-fatal overdoses are of clinical significance because a history of overdose strongly predicts future overdoses, thus those who overdosed

are likely to do so again (Darke et al., 1996; McGregor et al., 1998; Powis et al., 1999; Kerr et al., 2007). For this reason, I have tried to perform data linkage between CRIS and LAS so that data on fatal as well as non-fatal opioid overdose call-outs could be captured for analysis, thus providing important information of one's drug use behaviour and severity of risk. However, after discussions with the LAS and the data linkage team, this has proven unsuccessful due to the quality of electronic data (with some data remaining only in paper records) held by LAS, the volume of approvals, administrative tasks required and PhD time constraints.

Similarly, one of the major limitations in Chapters 6 and 7 is the inability to establish what happened to patients after their transfer of care. Consequently, I was not able to establish whether any failures had occurred during the period of transition itself, or whether any de-stabilisation occurred after a successful transition to the new care provider. This is an important question, which might have been successfully answered if data linkage with the third-party sector (e.g. non-NHS) was in place/possible.

Treatment provision in drug and alcohol services is extensive and complex. Patients, especially opioid dependent patients, enter, dropout, re-enter and transfer between services or prison frequently (Palmer et al., 2009), and capturing one's complete journey through services is problematic. Therefore, the need for novel integrated data linkages is great, as is the need for novel data extraction approaches.

The completeness of data relied on information entered by the NHS staff. Often, designated structured fields are not utilized by clinicians rather information is typed in free-text fields, resulting in difficulties in capturing this information using the CRIS front-end.

A range of NLP applications are in place to extract information from free-text, but these are specific and limited to those features in the text considered high priority for the research undertaken to date and development of new applications is extremely complex and labour intensive, for example, as that described by Kadra et al. (2015). Throughout this thesis, a significant amount of time was spent on manual data searches and manual data extractions. NLP, however, was extremely useful in extracting diagnosis information to supplement data from structured fields (performance of which is described and evaluated in Chapter 3). In Chapter 5 for example, for an additional 280 (6%) patients the earliest OUD diagnosis within the observation period was obtained from the free-text fields using NLP – patients who, otherwise, might not have been captured in this cohort. If I had relied solely on structured fields, these diagnosis dates would have either appeared later or potentially these patients not have been captured at all om this cohort.

8.5.3 CONFOUNDING

Confounding is a fundamental consideration in epidemiology and a central issue in any observational study design. Not all confounding can be controlled for and, ultimately, the best method for removing confounding effects is through randomization (Prince et al., 2003). However, randomization is limited ethically to interventions which might be beneficial but where no strong evidence exists one way or another (Prince et al., 2003). Randomizing "real-world" scenarios, especially the impact of provision of services is also problematic. In this thesis, as in other observational studies, potential confounding was addressed by adjustment.

Although no specific power calculation were performed in this thesis, complete patient EHRs available for analytical purposes for almost 5000 OUD patients potentially provided the statistical power to simultaneously control for a large number of potential confounders. Throughout the analysis, I was able to include a broad range of factors in multivariable analyses, including socio-demographic variables, clinically appraised risks, poly-substance use information, severity of drug use, physical health and psychiatric comorbidity. Although the sample size is considered a strength throughout the thesis, some analyses were possibly underpowered, as indicated by large confidence intervals (e.g. Table 4.6 or 7.3) and as mentioned in Chapter 4 where low number of comorbid SMI patients are present.

Diagnosis and socio-demographic information are routinely recorded in SLaM. NDTMS and TOP were excellent sources of information about the severity and patterns of drug use, and with high completion rates (95% and 89% respectively, see Chapter 3 for more details on TOP and NDTMS). The BRSA-A provided valuable source of risk information which was used in Chapters 5 and 7 as potential confounders (in addition to exposures of interest in Chapter 5).

Nonetheless, as with all observational studies, residual confounding is possible (e.g. smoking). Furthermore, my potential confounders included deprivation score rather than a direct measure of socio-economic status (calculations of which are explained in Chapter 3). Measures of physical and psychological health (included in models in Chapters 4 and 7) is a single and self-reported measure used as proxy indicators of physical health and problems with anxiety, depression and other emotional problems. The mean age at diagnosis (for example as seen in Chapter 4) was around 37 years, which does not reflect the "classic profile" of a heroin user who would normally approach services in their early 20s. This is

because data is limited to observation periods and may not reflect the true representative of age at *first* OUD diagnosis.

The NLP application searching free text annotations to establish patient's 'smoking status' (current, past or never) only returned data for 4.32% of patients (n=209 / 4,837) suggesting that an overwhelming majority of patients never smoked. This is unlikely to be an accurate reflection of smoking status in this patient group. Previous research indicates smoking reaches high levels in drug users, especially heroin using population (Cookson et al., 2014). However, this poor recording of patients smoking status within addiction was not surprising, as previous research identified that staff rated smoking treatment significantly less important than treatment of other substances and only 29% of staff thought it should be addressed early in a client's primary addiction treatment (Cookson et al., 2014). Consequently, smoking status derived from this NLP application, (although valid and reliable when used in other patient groups [Wu et al., 2013]) was excluded from this cohort.

HoNOS, a standard measure and widely used measure of patient wellbeing (Wing et al., 1998), reaches high completion rates across a number of diagnostic groups (e.g. 83% of all SLaM patients with schizoaffective disorder). In the OUD cohort, however, HoNOS completion rate was only 14%. Therefore, alternative sources of information were searched to supplement this information for inclusion as potential confounders.

8.6 CLINICAL AND POLICY IMPLICATIONS

Clinical staff, the policy makers and patients should be aware of risks associated with OST treatment, which have been noted in this thesis.

Psychiatric comorbidity is not only common amongst heroin users, but higher mortality rates are found in those with comorbid PD and AUD (Chapter 4). This is especially true for OUD patients with AUD whose rate of death by hepatic disease increases by more than sevenfold. However, the treatment of such patients can be problematic. For example, how best to respond to clients who are under the influence of alcohol when presenting for their medication? There is little guidance as to how best to respond to these circumstances (NTA, 2009) and, given the heightened mortality rates in this group, more guidance is needed.

Similarly, OUD patients with comorbid personality disorder have been shown to have increased rates of mortality, especially by liver-related disease (Chapter 4), but only a small proportion of dual-diagnosis patients actually receive treatment for both PD and OUD disorders (SAMHSA, 2012). Patients with co-occurring disorders can face challenges accessing treatment, as they may be excluded from mental health services if they admit to a substance abuse problem, and vice versa (SAMHSA, 2012). Care for this population needs to be properly coordinated within an integrated care pathway (Strang et al., 2014)

The need for integrated care is also partially reiterated in Chapter 5, which has shown elevated mortality in OUD patients where suicidality was present. Suicidality may be much more complex and problematic to address within the addictions services, and with the need for dual-diagnostic/multidisciplinary care plan approaches, addressing high levels of

underlying depression and other psychiatric comorbidities (Cantor et al., 2001; Darke, et al., 2007).

Rather than seeing people with dual diagnosis as having two main problems, it may be more effective to acknowledge that they have complex needs (Hughes, 2006). Consequently, mental health staff would require drug and alcohol awareness and training and vice versa, to ensure a shared philosophy and knowledge base. Identification of OUD-related risks alone, can be achieved using a simple and brief screening (i.e. BRSA-A), which could be made aware of across services.

Clinical staff and the commissioning bodies, also need to be aware of the increased (twofold) mortality risk associated with non-admission of OUD patients where suicidality was clinically assessed as present. This risk was no longer present in suicidal OUD patients who were admitted to services (Chapter 5). With this in mind, Chapter 6 reports that non-admission into services was largely due to loss of contact and transfers out of service/catchment area (and not because of clinician's decision).

Drop out from treatment (and relapse) and erratic engagement in services appears to be highly prominent in this patient group (Degenhardt et al., 2011; Zanis & Woody, 1998). OUD patients who are assessed as being at risk of suicide and subsequently disengage with current services may require more determined strategies for patient follow-ups and service transition due to their high risk of mortality.

Attention to hard-to-reach populations is an essential component of the healthcare provision in a locality. Addiction problems are often more prevalent among these populations and may

be complicating their condition (Strang et al., 2014). Without better outreach for these poorly engagaged groups, current policy will maintain inequalities for more vulnerable groups.

Finally, commissioning bodies and clinicians need to be aware of the marked excess of overdose deaths after transfers of patients and their care despite continuation of OST (see Chapters 6 and 7). In Chapter 6 it was found that of those patients who died following a transfer, large subgroups included patients transitioned from secondary to primary care or to large independent care-provider organisations who had secured new NHS contracts after the introduction of competitive tendering procedures (DoH, 2013). If the purpose of such re-organisation is to achieve greater effectiveness and more cost-effective use of resources, then it might have been expected that we would find successful transfer of patients and their treatments, patient stability, and stable or lowered risk of mortality (Darke et al., 2005); however, these analysis instead indicated a high number of fatal overdoses particularity in the first month post-transfer. Therefore, more consideration should be taken when re-commissioning is proposed; and, if carried out, effective overdose prevention strategies should be in place during periods of patient transfer.

In fact, any transfer of patients whether due to escalation of treatment (e.g. to an inpatient unit) or as part of successful recovery (e.g. from secondary to primary care) needs to be undertaken with caution, similar to that which occurs at the time of discharge from services following successful detoxification from any opioids. One way of potentially minimising overdose risk in such situations is the pre-provision of naloxone. This, however, comes with its own legislative and organizational challenges requiring revision (Strang, 2015).

8.7 FURTHER RESEARCH RECOMMENDATIONS

8.7.1 IMMEDIATE RESEARCH QUESTIONS

Several questions remain unanswered due to the limitations of data or are beyond the scope of this thesis. First, what happened to patients who were transferred out of services to continue their treatment elsewhere? Did they successfully transition to the alternative service or drop out in the process? Significantly higher levels of mortality were found in patients who were transferred from SLaM but establishing answers to the above questions was not possible at present.

Moreover, crude analyses indicate high clustering of deaths in the first month post-transfer. Is this still the case after adjustment using multivariable methods of analysis? Are transient risks post-transfer similar to that on post-discharge or post-prison release (Cornish et al., 2010; Davoli et al., 2007; Farrell & Marsden, 2008; Singleton, 2003)? If so, what are the mechanisms behind these excess deaths? Are these also attributed to the loss of tolerance after a subsequent relapse (Strang et al., 2003)? These results need deeper and wider exploration. Answers to these questions are urgently needed and further research should focus on replicating these results and expand analysis to fully capture the transition processes.

Despite the relatively large cohort, the number of deaths within those with SMI comorbidity was small and important effects might have been missed. Future research should explore these associations further using larger samples. Similarly, ICD-10 diagnosis of depression were not included in the analysis in Chapter 4 and a proxy measure was used instead. Low numbers of OUD+depression patients were surprising and suggest either under-reporting of

symptoms by patients or lack of initiative to evaluate symptoms and diagnose patients from the clinical staff. Further research should be carried out in this area to further strengthen the argument for improved availability and provision of dual-diagnostic services.

The relatively small OUD+PD sample put limits on power for further and more detailed analysis. Although higher mortality risks have been identified, it is still unclear exactly which personality disorders are problematic. To aid in the understanding of mortality risk in this group, further research should focus on differences between the types of personality disorders, and with a particular focus on directions of casualty (i.e. longitudinal analysis) to establish whether PD is particularly harmful to opioid users or the use of opioids aggravates a pre-existing PD.

Finally, the BRSA-A was not formally evaluated as a measurement in terms of constructs such as inter-rater or test–retest reliability, or its discriminant validity. However, this is a "real-world" measure, developed by clinicians and is actively used in daily practice, and results (Chapter 5) suggest its effectiveness in highlighting those at highest risk. Further evaluations of the scale is a worthwhile research target, if the scale was to be introduced across mental health services.

8.7.2 THE LONG TERM VIEW

Integration and extraction of data

First, the continuity of integration of datasets is important. National records data linkages are needed as these enable statistically powerful studies to ascertain which specific causes of

death are elevated and to identify the key behavioral and demographic risk factors. For example, the Drug Data Warehouse (Millar et al., 2012; Pierce et al., 2015) - an anonymous, case-linked collection of secondary datasets about substance users in England and Wales. This is the largest opioid user cohort with cause specific mortality, with almost 200,000 opioid users represented on the system; incorporating data from drug treatment services, prison and probation services, criminal justice referral, and drug testing on arrest schemes. Capturing one's journey through dependence and recovery is a long and complex process, and integration of data would allow for highly informative continuity of research in opioid dependence.

Similarly, at the time of its development, the CRIS database contained 123 000 cases and the CRIS application was primarily restricted to that imposed by the format of the source EHR fields. Since then, the SLaM BRC Case Register has expanded substantially, not only in case numbers (now over 280 000) but also, most importantly, in the scale and depth of derived and externally linked information available. A priority for development has been to continue the integration of external data and to develop more efficient ways of using open-text data using NLP (Perera et al., 2015). If the obstacles described earlier could be overcome then a linkage of LAS data with CRIS would not only provide much needed information surrounding non-fatal overdoses but might also be beneficial in research within other mental health disorders.

Furthermore, much time was spent on manual retrieval of data surrounding the circumstances of deaths. It is near impossible to manually code free text fields on a large scale due to time and labour constrains. Without the continuous development of NLP applications, much information "buried" in free text fields would not be accessible in a systematic way. NLP applications specific to addictions services should be developed to enable researchers to

retrieve crucial information placed within the free-text fields. While the process of linking data and development of individual NLP applications is long and complex, it almost certainly is worth the effort.

Personalized treatment approach

People with OUD often present to treatment services with varying levels of addiction severity and many have coexisting health and social problems which follow addiction onset, or are independent of the primary disorder (Kleber et al., 2007). Data from numerous studies indicate that there are large individual differences in patients, for example, in their response to most effective treatments that have been standardized and with therapists who adhere closely to treatment manuals (McKay, 2009).

Despite these considerable variations in patient dependence severity and individual differences, most treatments in the addictions strive to deliver essentially the same 'blanket approach' intervention to all patients, regardless of circumstances surrounding their treatment, history and personal factors; and without effective evaluations of risk, especially the risk of overdose and mortality (Marsden et al., 2014).

The variability in patients highlights the need for adaptive models of care—that is, tailored interventions that specify treatment modifications triggered by the patient's individual characteristics, treatment history, treatment response and changes in symptoms (McKay, 2009).

With existing literature and results from this thesis, a relatively good knowledge base on mortality risk factors in opioid dependency exists and the availability of electronic health data in mental health has opened doors to treatment innovations, through the availability and integration of relevant information at the point of care (Costa et al., 2009; Kawamoto, et al., 2005; Schreiber & Giustini, 2009).

Information management systems which facilitate the making of decisions by clinicians have been well-established in the clinical arena for more than forty years (de Dombal et al., 1972). However, prognostic modelling of possible outcomes using multivariate models, and drawing on recent technical developments such as natural language processing and electronic health records, whilst feeding information to a clinician in real-time has not been developed for addictions services.

Prognostic models are often too complex for daily use in clinical settings without computer support. However, the introduction of computerised patient records, such as ePJS can enable not only the development and validation of such risk-profile modelling but also facilitate their application in routine care (James, 2001; Kawamoto et al., 2005).

Firstly, however, a consultation and a technical appraisal of such novel clinical decision-making tool should be carried out with the NHS clinical staff, for example semi-structured interviews might be undertaken. This exercise would assess the utility and acceptability of electronic patient risk profiles; and establish satisfactory standards and clinical requirements to maximize its usefulness by determining the type and form of risk information that the clinicians would find most useful. I obtained necessary approvals (including KCL ethics and R&D approvals; borough lead and gatekeeper approvals) and supporting documents

(including participant information leaflet, consent form, indicative interview process) are already obtained as part of this PhD (see appendix vii. for KCL ethics approval). The work however was beyond the current scope of thesis as other research questions (as presented in Chapter 6) took priority.

8.8 CONCLUSIONS

In conclusion, the findings of this thesis provide evidence of the burden of opioid use disorder in secondary mental health services and the general population. Individual as well as service-related risks have been identified.

The elevated risks of all-cause and/or overdose and liver-related mortality were associated with OUD patients with comorbid PD and who misuse alcohol. This highlights the need for assessment of psychiatric comorbidity and poly-substance use, and improvement of integrated care.

Further mortality risks were found in suicidal OUD patients who were not admitted to services; in patients who were discharged from OST services or dropped out; and in those who were transferred between services to continue their OST elsewhere.

The risks associated with discharge and transfer were particularly prominent in the first month after leaving SLaM. These results highlight risks associated with re-commissioning of addictions services and the need to implement effective overdose prevention strategies in such situations.

Finally, the study found an effective addictions-related measure which may be helpful to efficiently identify OUD patients at heightened risk, which could be adapted for services outside addictions.

REFERENCES

Advisory Council on the Misuse of Drugs (ACMD). (2015). How can opioid substitution therapy (and drug treatment and recovery systems) be optimised to maximise recovery outcomes for service users? London. [Date of retrieval 05January2017]

American Psychiatric Association (APA). (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR*. (American Psychiatric Association, Ed.). Washington, DC.

American Psychiatric Association (APA). (2013). Diagnostic and statistical manual of mental disorders (5th Edition). Arlington, VA: APA.

Amundsen, E. J. (2015). Drug-related causes of death: Socioeconomic and demographic characteristics of the deceased. Scandinavian Journal of Public Health, 43(6), 571–579. http://doi.org/10.1177/1403494815585909

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative Epidemiology of Dependence on Tobacco, Alcohol, Controlled Substances, and Inhalants: Basic Findings From the National Comorbidity Survey. *Experimental and Clinical Psycho Pharmacology*, *2*(3), 244–268.

Arendt, M., Munk-Jorgensen, P., Sher, L., & Jensen, S. O. (2011). Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment. Drug Alcohol Depend, 114(2–3), 134–139. http://doi.org/10.1016/j.drugalcdep.2010.09.013

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., & Munk-Jorgensen, P. (2007). Psychopathology among cannabis-dependent treatment seekers and association with later substance abuse treatment. J Subst Abuse Treat, 32(2), 113–119. http://doi.org/10.1016/j.jsat.2006.07.005

Bargagli, A. M., Davoli, M., Minozzi, S., Vecchi, S., & Perucci, C. a. (2007). A Systematic Review of Observational Studies on Treatment of Opioid Dependence.

Bargagli, A. M., Hickman, M., Davoli, M., Perucci, C. A., Schifano, P., Buster, M., … Vicente, J. (2006). Drug-related mortality and its impact on adult mortality in eight European countries. The European Journal of Public Health, 16(2).

Bargagli, A. M., Sperati, A., Davoli, M., Forastiere, F., & Perucci, C. A. (2001). Mortality among problem drug users in Rome: an 18-year follow-up study, 1980-97. Addiction, 96(10), 1455–1463. http://doi.org/10.1080/09652140120075189

Bartu, A., Freeman, N. C., Gawthorne, G. S., Codde, J. P., & Holman, C. D. (2004). Mortality in a cohort of opiate and amphetamine users in Perth, Western Australia. Addiction, 99(1), 53–60.

Bell, J., Shanahan, M., Mutch, C., Rea, F., Ryan, A., Batey, R., … Winstock, A. (2007). A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence. Addiction, 102(12), 1899–1907. http://doi.org/10.1111/j.1360-0443.2007.01979.x

Berridge, V. (2009). Heroin prescription and history. *The New England Journal of Medicine*, *361*(8), 820–1. http://doi.org/10.1056/NEJMe0904243

Berridge, V., & Edwards, G. (1981). *Opium and the people : opiate use in nineteenth-century England*. A. Lane.

Berridge, V., & Mars, S. (2004). History of addictions. *Journal of Epidemiology and Community Health*, *58*(9), 747–50. http://doi.org/10.1136/jech.2003.015370

Best, D., Gossop, M., Man, L.-H., Finch, E., Greenwood, J., & Strang, J. (2000). Accidental and deliberate overdose among opiate addicts in methadone maintenance treatment: are deliberate overdoses systematically different? *Drug and Alcohol Review*, *19*(2), 213–216. http://doi.org/10.1080/713659326

Bird, S. M. (2008). Changes in male suicides in Scottish prisons: 10-year study. The British Journal of Psychiatry, 192(6), 446–449. http://doi.org/10.1192/bjp.bp.107.038679

Bird, S. M., & Hutchinson, S. J. (2003). Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996-99. Addiction (Abingdon, England), 98(2), 185–90. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12534423

Bird, S. M., Fischbacher, C. M., Graham, L., & Fraser, A. (2015). Impact of opioid substitution therapy for Scotland's prisoners on drug-related deaths soon after prisoner release. Addiction (Abingdon, England), 110(10), 1617–24. http://doi.org/10.1111/add.12969

Bjornaas, M. A., Jacobsen, D., Haldorsen, T., & Ekeberg, O. (2009). Mortality and causes of death after hospital-treated self-poisoning in Oslo: A 20-year follow-up. Clinical Toxicology, 47(2), 116–123. http://doi.org/10.1080/15563650701771981

Bogdanowicz, K. M., Stewart, R., Broadbent, M., Hatch, S. L., Hotopf, M., Strang, J., & Hayes, R. D. (2015). Double trouble: Psychiatric comorbidity and opioid addiction-all-cause and cause-specific mortality. *Drug and Alcohol Dependence*, *148*, 85–92. http://doi.org/10.1016/j.drugalcdep.2014.12.025

Breen, C. L., Harris, S. J., Lintzeris, N., Mattick, R. P., Hawken, L., Bell, J., … Mendoza, E. (2003). Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug and Alcohol Dependence*, *71*(1), 49–55. http://doi.org/10.1016/S0376-8716(03)00071-1

Britton, P. C., Wines, J. D., & Conner, K. R. (2010). Non-fatal overdose in the 12 months following treatment for substance use disorders. *Drug and Alcohol Dependence*, *107*(1), 51–55. http://doi.org/10.1016/j.drugalcdep.2009.09.005

Brooner, R. K., King, V. L., Kidorf, M., Schmidt Jr., C. W., & Bigelow, G. E. (1997). Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch Gen Psychiatry*, *54*(1), 71–80.

Brownstein, M. J. (1993). A brief history of opiates, opioid peptides, and opioid receptors. *Proc. Natl. Acad. Sci*, *90*, 5391–5393.

Brugal, M. T., Barrio, G., De, L. F. L., Regidor, E., Royuela, L., & Suelves, J. M. (2002). Factors associated with non-fatal heroin overdose: assessing the effect of frequency and route of heroin administration. Addiction (Abingdon, England), 97(3), 319–27. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11964108

Brugal, M. T., Domingo-Salvany, A., Puig, R., Barrio, G., Garcia de Olalla, P., & de la Fuente, L. (2005). Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction*, *100*(7), 981–989. http://doi.org/10.1111/j.1360-0443.2005.01089.x

Cacciola, J. S., Alterman, A. I., Rutherford, M. J., McKay, J. R., & Mulvaney, F. D. (2001). The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend*, *61*(3), 271–280.

Cantor, C., McTaggart, P., & De Leo, D. (2001). Misclassification of suicide-the contribution of opiates. *Psychopathology*, *34*(3), 140–6. http://doi.org/49297

Caplehorn, J. R., Dalton, M. S., Haldar, F., Petrenas, A. M., & Nisbet, J. G. (1996). Methadone maintenance and addicts' risk of fatal heroin overdose. Substance Use & Misuse, 31(2), 177–96. http://doi.org/10.3109/10826089609045806

Carpenter, M. J., Chutuape, M. A., & Stitzer, M. L. (1998). Heroin snorters versus injectors: comparison on drug use and treatment outcome in age-matched samples. *Drug and Alcohol Dependence*, *53*(1), 11–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10933336

Chang, C.-K., Hayes, R. D., Broadbent, M., Fernandes, A. C., Lee, W., Hotopf, M., & Stewart, R. (2010). All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry, 10(1), 77. http://doi.org/10.1186/1471-244X-10-77

Chen, K., & Kandel, D. B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. *American Journal of Public Health*, *85*(1), 41–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7832260

Clausen, T., Anchersen, K., & Waal, H. (2008). Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study. Drug and Alcohol Dependence, 94(1), 151–157. http://doi.org/10.1016/j.drugalcdep.2007.11.003

Coffin, P. O., Tracy, M., Bucciarelli, A., Ompad, D., Vlahov, D., & Galea, S. (2007). Identifying injection drug users at risk of nonfatal overdose. Acad Emerg Med, 14(7), 616–623. http://doi.org/10.1197/j.aem.2007.04.005

Compton, W. M., Conway, K. P., Stinson, F. S., Colliver, J. D., & Grant, B. F. (2005). Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. The Journal of Clinical Psychiatry, 66(6), 677–85. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15960559

Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R. J., … Taylor, R. S. (2007). Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*, *11*(9), 1–171, iii–iv. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17313907

Cookson, C., Strang, J., Ratschen, E., Sutherland, G., Finch, E., & McNeill, A. (2014). Smoking and its treatment in addiction services: Clients' and staff behaviour and attitudes. BMC Health Services Research, 14(1), 304. http://doi.org/10.1186/1472-6963-14-304

Cornish J.; Strang, J.; Vickerman, P.; Hickman, M., R. . M. (2010). Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *Bmj*, *341*. http://doi.org/doi:10.1136/bmj.c5475

Costa, B. M., Fitzgerald, K. J., Jones, K. M., & Dunning Am, T. (2009). Effectiveness of IT-based diabetes management interventions: a review of the literature. *BMC Fam Pract*, *10*, 72. http://doi.org/10.1186/1471-2296-10-72

Cousins, G., Boland, F., Courtney, B., Barry, J., Lyons, S., & Fahey, T. (2016). Risk of mortality on and off methadone substitution treatment in primary care: a national cohort study. Addiction, 111(1), 73–82. http://doi.org/10.1111/add.13087

Cousins, G., Teljeur, C., Motterlini, N., McCowan, C., Dimitrov, B. D., & Fahey, T. (2011). Risk of drug-related mortality during periods of transition in methadone maintenance treatment: a cohort study. Journal of Substance Abuse Treatment, 41(3), 252–60. http://doi.org/10.1016/j.jsat.2011.05.001

Cox, D. R. (1972). Regression Models and Life-Tables. Journal of the Royal Statistical Society, 34(2), 187–220.

Crime Survey for England and Wales. (2015). *Drug Misuse: Findings from the 2014/15 Crime Survey for England and Wales*. London, UK.

Darke, S. (2011). The life of the heroin user : typical beginnings, trajectories and outcomes. Cambridge University Press.

Darke, S., & Hall, W. (2003). Heroin overdose: research and evidence-based intervention. J Urban Health, 80(2), 189–200. http://doi.org/10.1093/jurban/jtg022

Darke, S., & Ross, J. (1997). Polydrug dependence and psychiatric comorbidity among heroin injectors. Drug and Alcohol Dependence, 48(2), 135–41. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9363413

Darke, S., & Ross, J. (2000). The relationship between suicide and overdose among methadone maintenance patients. Australia.

Darke, S., & Ross, J. (2001). The relationship between suicide and heroin overdose among methadone maintenance patients in Sydney, Australia. *Addiction (Abingdon, England)*, *96*(10), 1443–53. http://doi.org/10.1080/09652140120075170

Darke, S., & Ross, J. (2002). Suicide among heroin users: rates, risk factors and methods. *Addiction*, *97*(11), 1383–1394.

Darke, S., & Zador, D. (1996). Fatal heroin "overdose": a review. *Addiction (Abingdon, England)*, *91*(12), 1765–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8997759

Darke, S., Degenhardt, L., & Mattick, R. (2007). *Mortality amongst Illicit Drug Users: epidemiology, causes and intervention.* Cambridge, UK: Cambridge University Press.

Darke, S., Duflou, J., & Torok, M. (2010). The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. *Drug and Alcohol Dependence*, *106*(1), 1–6. http://doi.org/10.1016/j.drugalcdep.2009.07.014

Darke, S., Hall, W., & Swift, W. (1994). Prevalence, symptoms and correlates of antisocial personality disorder among methadone maintenance clients. Drug and Alcohol Dependence, 34(3), 253–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8033764

Darke, S., Kaye, S., & Duflou, J. (2006). Systemic disease among cases of fatal opioid toxicity. *Addiction*, *101*(9), 1299–1305. http://doi.org/10.1111/j.1360-0443.2006.01495.x

Darke, S., Mattick, R. P., & Degenhardt, L. (2003). The ratio of non-fatal to fatal heroin

overdose. *Addiction*, *98*(8), 1169–1171. http://doi.org/10.1046/j.1360-0443.2003.00474.x

Darke, S., Ross, J., & Teesson, M. (2005). Twelve-month outcomes for heroin dependence treatments: does route of administration matter? *Drug and Alcohol Review*, *24*(2), 165–171. http://doi.org/10.1080/09595230500102657

Darke, S., Ross, J., Zador, D., & Sunjic, S. (2000). Heroin-related deaths in regional New South Wales, 1992-96. *Drug and Alcohol Review*, *19*(1), 35–40. http://doi.org/10.1080/09595230096129

Darke, S., Williamson, A., Ross, J., & Teesson, M. (2005). Non-fatal heroin overdose, treatment exposure and client characteristics: findings from the Australian treatment outcome study (ATOS). *Drug Alcohol Rev*, *24*(5), 425–432. http://doi.org/10.1080/09595230500286005

Davidson, P. J., McLean, R. L., Kral, A. H., Gleghorn, A. A., Edlin, B. R., & Moss, A. R. (2003). Fatal heroin-related overdose in San Francisco, 1997-2000: a case for targeted intervention. *Journal of Urban Health : Bulletin of the New York Academy of Medicine*, *80*(2), 261–73. http://doi.org/10.1093/jurban/jtg029

Davoli, M., Bargagli, A. M., Perucci, C. A., Schifano, P., Belleudi, V., Hickman, M., … Faggiano, F. (2007). Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. *Addiction*, *102*(12), 1954–1959. http://doi.org/10.1111/j.1360-0443.2007.02025.x

Davoli, M., Perucci, C. A., Forastiere, F., Doyle, P., Rapiti, E., Zaccarelli, M., & Abeni, D. D. (1993). Risk factors for overdose mortality: a case-control study within a cohort of intravenous drug users. Int J Epidemiol, 22(2), 273–277.

Davoli, M., Perucci, C. A., Rapiti, E., Bargagli, A. M., D'Ippoliti, D., Forastiere, F., & Abeni, D. (1997). A persistent rise in mortality among injection drug users in Rome, 1980 through 1992. American Journal of Public Health, 87(5), 851–3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9184520

de Dombal, F. T., Leaper, D. J., Staniland, J. R., McCann, A. P., & Horrocks, J. C. (1972). Computer-aided diagnosis of acute abdominal pain. *Br Med J*, *2*(5804), 9–13.

Degenhardt, L., & Hall, W. (2012). Extent of illicit drug use and dependence, and their contribution to the global burden of disease. The Lancet, 379(9810), 55–70. http://doi.org/10.1016/S0140-6736(11)61138-0

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2010). Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*, *106*(1), 32–51. http://doi.org/10.1111/j.1360-0443.2010.03140.x

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction, 106(1), 32–51. http://doi.org/10.1111/j.1360-0443.2010.03140.x

Degenhardt, L., Charlson, F., Mathers, B., Hall, W. D., Flaxman, A. D., Johns, N., & Vos, T. (2014b). The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction*, *109*(8), 1320–1333. http://doi.org/10.1111/add.12551

Degenhardt, L., Larney, S., Kimber, J., Gisev, N., Farrell, M., Dobbins, T., … Burns, L. (2014a). The impact of opioid substitution therapy on mortality post-release from prison: retrospective data linkage study. *Addiction*, *109*(8), 1306–1317. http://doi.org/10.1111/add.12536

Degenhardt, L., Lynskey, M., & Hall, W. (2000). Cohort trends in the age of initiation of drug use in Australia. *Australian and New Zealand Journal of Public Health*, *24*(4), 421–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11011471

Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T., & Burns, L. (2009). Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. *Drug and Alcohol Dependence*, *105*(1), 9–15. http://doi.org/10.1016/j.drugalcdep.2009.05.021

Dennis, M. L., Scott, C. K., Funk, R., & Foss, M. A. (2005). The duration and correlates of addiction and treatment careers. Journal of Substance Abuse Treatment, 28(2), S51–S62. http://doi.org/10.1016/j.jsat.2004.10.013

Department of Health (DOH). (2007). Drug Misuse and Dependence: UK Guidelines on Clinical Management, *32*(9), 360–360. http://doi.org/10.1192/pb.bp.108.021287

Department of Health (DOH). (2013). *Changes to the National Health Service (Procurement, Patient Choice and Competition) Regulations 2013.* London, UK.

Dickey, B., Dembling, B., Azeni, H., & Normand, S. L. (2004). Externally caused deaths for adults with substance use and mental disorders. J Behav Health Serv Res, 31(1), 75–85.

Diekstra, R. F., & Gulbinat, W. (1993). The epidemiology of suicidal behaviour: a review of three continents. *World Health Statistics Quarterly. Rapport Trimestriel de Statistiques Sanitaires Mondiales*, *46*(1), 52–68. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7694430

Dinwiddie, S. H., Reich, T., & Cloninger, C. R. (1992). Psychiatric comorbidity and suicidality among intravenous drug users. J Clin Psychiatry, 53(10), 364–369.

Disney, E., Kidorf, M., Kolodner, K., King, V., Peirce, J., Beilenson, P., & Brooner, R. K. (2006). Psychiatric comorbidity is associated with drug use and HIV risk in syringe exchange participants. J Nerv Ment Dis, 194(8), 577–583. http://doi.org/10.1097/01.nmd.0000230396.17230.28

DrugScope. (2015). State of the Sector 2014-15 -Summary Report. London.

Dwarakanath, S. (1965). Use of opium and cannabis in the traditional systems of medicine in India. *UNODC Bulletin*, 15–19. Retrieved from https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1965-01-01_1_page004.html

European Monitoring Centre for Drugs and Drug Addiction. (2010). Annual report on the state of the drugs problem in Europe. Lisbon. Retrieved from http://www.emcdda.europa.eu/publications/annual-report/2010 [Date of retrieval 05January2017]

European Monitoring Centre for Drugs and Drug Addiction. (2015). EMCDDA | Heroin profile. Retrieved from http://www.emcdda.europa.eu/publications/drug-profiles/heroin. [Date of retrieval 05January2017]

European Monitoring Centre for Drugs and Drugs Prevention. (2016). *Hepatitis C among drug users in Europe: epidemiology, treatment and prevention*. Lisbon. Retrieved from http://www.emcdda.europa.eu/publications/insights/hepatitis-c-among-drug-users-in-

europe. [Date of retrieval 05January2017].
Faggiano, F., Vigna-Taglianti, F., Versino, E., & Lemma, P. (2003). Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev, (3), Cd002208. http://doi.org/10.1002/14651858.cd002208
Farrell, M., & Marsden, J. (2008). Acute risk of drug-related death among newly released prisoners in England and Wales. *Addiction (Abingdon, England)*, *103*(2), 251–5. http://doi.org/10.1111/j.1360-0443.2007.02081.x
Flynn, P. M., Joe, G. W., Broome, K. M., Simpson, D. D., & Brown, B. S. (2003). Recovery from opioid addiction in DATOS. *Journal of Substance Abuse Treatment*, *25*(3), 177–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14670523
Fok, M. L.-Y., Hayes, R. D., Chang, C.-K., Stewart, R., Callard, F. J., & Moran, P. (2012). Life expectancy at birth and all-cause mortality among people with personality disorder. Journal of Psychosomatic Research, 73(2), 104–107. http://doi.org/10.1016/j.jpsychores.2012.05.001
Ford, E., Carroll J.A., Smith, H.E., Scott, D., Cassell, J.A. (2016). Extracting informationfrom the text f electronic medical records to improve case detection: a systematic review. *Journal of the American Medical Informatics Association, 23(5), 1007-1015.* http://doi.org/10.1093/jamia/ocv180
Fort, J. (1965). Giver of delight or liberator of sin: Drug use and "addiction" in Asia. *Bull Narc*, *17*, 1–11.
Fugelstad, A., Agren, G., & Romelsjö, A. (1998). Changes in Mortality, Arrests, and Hospitalizations in Nonvoluntary Treated Heroin Addicts in Relation to Methadone Treatment. Substance Use & Misuse, 33(14), 2803–2817. http://doi.org/10.3109/10826089809059352
Fugelstad, A., Ahlner, J., Brandt, L., Ceder, G., Eksborg, S., Rajs, J., & Beck, O. (2003). Use of morphine and 6-monoacetylmorphine in blood for the evaluation of possible risk factors for sudden death in 192 heroin users. Addiction (Abingdon, England), 98(4), 463–70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12653816
Fugelstad, A., Jo Van Rajs, /, Bottiger, M., Gerhardsson, M., & Verdier, D. (1995). Mortality among HIV-infected intravenous drug addicts in Stockholm in relation to methadone treatment. Addiction, 90, 711–716.
Ghodse, A. H., Sheehan, M., Taylor, C., & Edwards, G. (1985). Deaths of drug addicts in the United Kingdom 1967-81. Br Med J (Clin Res Ed), 290(6466), 425–428.
Ghodse, H. (2002). *Drugs and Addictive Behaviour-A Guide to Treatment.* Cambridge, UK: Cambridge University Press.
Ghodse, H., Oyefeso, A., & Kilpatrick, B. (1998). Mortality of drug addicts in the United Kingdom 1967-1993. Int J Epidemiol, 27(3), 473–478.
Goodman, L. ., & Gillman, A. G. (1996). *Goodman & Gilman's the pharmacological basis of therapeutics.* (9th editio). New York, USA: McGraw Hill.
Gossop, M., Griffiths, P., Powis, B., & Strang, J. (1992). Severity of dependence and route of administration of heroin, cocaine and amphetamines. *British Journal of Addiction*, *87*(11), 1527–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1458032
Gossop, M., Griffiths, P., Powis, B., Williamson, S., & Strang, J. (1996). Frequency of non-fatal heroin overdose: survey of heroin users recruited in non-clinical settings. *BMJ*,

313.

Gossop, M., Stewart, D., Treacy, S., & Marsden, J. (2002). A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. Addiction, 97(1), 39–47.

Haasen, C., Verthein, U., Degkwitz, P., Berger, J., Krausz, M., & Naber, D. (2007). Heroin-assisted treatment for opioid dependence. The British Journal of Psychiatry, 191(1).

Hahné, S. J. M., Veldhuijzen, I. K., Wiessing, L., Lim, T.-A., Salminen, M., & Laar, M. van de. (2013). Infection with hepatitis B and C virus in Europe: a systematic review of prevalence and cost-effectiveness of screening. *BMC Infectious Diseases*, *13*, 181. http://doi.org/10.1186/1471-2334-13-181

Hardwood, H. (1990). The Effectiveness of Treatment. National Academies Press (US).

Harris, E. C., & Barraclough, B. (1997). Suicide as an outcome for mental disorders. A meta-analysis. *The British Journal of Psychiatry : The Journal of Mental Science*, *170*, 205–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9229027

Harris, E. C., & Barraclough, B. (1998). Excess mortality of mental disorder. Br J Psychiatry, 173, 11–53.

Harriss, L., & Hawton, K. (2005). Suicidal intent in deliberate self-harm and the risk of suicide: the predictive power of the Suicide Intent Scale. Journal of Affective Disorders, 86(2–3), 225–33. http://doi.org/10.1016/j.jad.2005.02.009

Hayes, R. D., Chang, C. K., Fernandes, A., Begum, A., To, D., Broadbent, M., … Stewart, R. (2012). Associations between symptoms and all-cause mortality in individuals with serious mental illness. J Psychosom Res, 72(2), 114–119. http://doi.org/10.1016/j.jpsychores.2011.09.012

Hayes, R. D., Chang, C. K., Fernandes, A., Broadbent, M., Lee, W., Hotopf, M., & Stewart, R. (2011). Associations between substance use disorder sub-groups, life expectancy and all-cause mortality in a large British specialist mental healthcare service. Drug Alcohol Depend, 118(1), 56–61. http://doi.org/10.1016/j.drugalcdep.2011.02.021

Hayes, R. D., Downs, J., Chang, C.-K., Jackson, R. G., Shetty, H., Broadbent, M., … Stewart, R. (2015). The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. Schizophrenia Bulletin, 41(3), 644–55. http://doi.org/10.1093/schbul/sbu120

Hickman, M., Macleod, J., & Degenhardt, L. (2016). Commentary on Cousins et al . (2016): Accumulating evidence on risk of mortality on and off opioid substitution treatment. Addiction, 111(1), 83–84. http://doi.org/10.1111/add.13185

Hickman, M., Madden, P., Henry, J., Baker, A., Wallace, C., Wakefield, J., … Elliott, P. (2003). Trends in drug overdose deaths in England and Wales 1993-98: methadone does not kill more people than heroin. Addiction (Abingdon, England), 98(4), 419–25. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12653812

Hind, C. R. (1990). Pulmonary complications of intravenous drug misuse. 1. Epidemiology and non-infective complications. *Thorax*, *45*(11), 891–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2256022

Hser, Y. I., Grella, C. E., Hsieh, S. C., Anglin, M. D., & Brown, B. S. (1999). Prior treatment experience related to process and outcomes in DATOS. *Drug and Alcohol Dependence*, *57*(2), 137–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10617098

Hser, Y. I., Hoffman, V., Grella, C. E., & Anglin, M. D. (2001). A 33-year follow-up of narcotics addicts. Archives of General Psychiatry, 58(5), 503–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11343531

Hughes, L. (2006). Closing the gap: a capability framework for working effectively with people with combined mental health and substance use problems (dual diagnosis).

James, B. C. (2001). Making It Easy to Do It Right. *New England Journal of Medicine*, *345*(13), 991–993. http://doi.org/10.1056/NEJM200109273451311

Johnson, C., Dong, H., Ahamad, K., Hayashi, K., Milloy, M. J., Kerr, T., & Wood, E. (2015). Impact of binge alcohol on mortality among people who inject drugs. *Addictive Behaviors Reports*, *2*, 28–32. http://doi.org/10.1016/j.abrep.2015.05.002

Jones, J. D., Mogali, S., & Comer, S. D. (2012). Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence*, *125*(1–2), 8–18. http://doi.org/10.1016/j.drugalcdep.2012.07.004

Kadra, G., Stewart, R., Shetty, H., Jackson, R. G., Greenwood, M. A., Roberts, A., … Hayes, R. D. (2015). Extracting antipsychotic polypharmacy data from electronic health records: developing and evaluating a novel process. *BMC Psychiatry*, *15*(1), 166. http://doi.org/10.1186/s12888-015-0557-z

Kapur, N. (2005). Management of self-harm in adults: which way now? The British Journal of Psychiatry : The Journal of Mental Science, 187(6), 497–9. http://doi.org/10.1192/bjp.187.6.497

Kariminia, A., Butler, T., Corben, S., Levy, M., Grant, L., Kaldor, J., & Law, M. (2007). Extreme cause-specific mortality in a cohort of adult prisoners--1988 to 2002: a data-linkage study. International Journal of Epidemiology, 36(2), 310–316. http://doi.org/10.1093/ije/dyl225

Kawamoto, K., Houlihan, C. A., Balas, E. A., & Lobach, D. F. (2005). Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ, 330(7494).

Kerr, T., Fairbairn, N., Tyndall, M., Marsh, D., Li, K., Montaner, J., & Wood, E. (2007). Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. Drug Alcohol Depend, 87(1), 39–45. http://doi.org/10.1016/j.drugalcdep.2006.07.009

Khantzian, E. J., & Treece, C. (1985). DSM-III psychiatric diagnosis of narcotic addicts. Recent findings. Arch Gen Psychiatry, 42(11), 1067–1071.

King, L. (2009). Forensic Chemistry of Substance Misuse. RSC Publishing.

King, C. A., & Merchant, C. R. (2008). Social and interpersonal factors relating to adolescent suicidality: a review of the literature. *Archives of Suicide Research : Official Journal of the International Academy for Suicide Research*, *12*(3), 181–96. http://doi.org/10.1080/13811110802101203

King, V. L., Kidorf, M. S., Stoller, K. B., & Brooner, R. K. (2000). Influence of psychiatric comorbidity on HIV risk behaviors: changes during drug abuse treatment. J Addict Dis, 19(4), 65–83. http://doi.org/10.1300/J069v19n04_07

Kleber, H. D., Weiss, R. D., Anton Jr., R. F., George, T. P., Greenfield, S. F., Kosten, T. R., … Regier, D. (2007). Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry, 164(4 Suppl), 5–123.

Krach, S. (2002). *Karch's Pathology of Drug Abuse* (4th edition). Boca Raton: CRC Press.
Krausz, M., Verthein, U., & Degkwitz, P. (1999). Psychiatric comorbidity in opiate addicts. Eur Addict Res, 5(2), 55–62. http://doi.org/18966
Landheim, A. S., Bakken, K., & Vaglum, P. (2006). Impact of comorbid psychiatric disorders on the outcome of substance abusers: a six year prospective follow-up in two Norwegian counties. BMC Psychiatry, 6, 44. http://doi.org/10.1186/1471-244x-6-44
Larney, S., Gisev, N., Farrell, M., Dobbins, T., Burns, L., Gibson, A., … Degenhardt, L. (2014). Opioid substitution therapy as a strategy to reduce deaths in prison: retrospective cohort study. BMJ Open, 4(4), e004666. http://doi.org/10.1136/bmjopen-2013-004666
Lee, C. T. C., Chen, V. C. H., Tan, H. K. L., Chou, S.-Y., Wu, K.-H., Chan, C.-H., & Gossop, M. (2013). Suicide and other-cause mortality among heroin users in Taiwan: A prospective study. Addictive Behaviors, 38, 2619–2623. http://doi.org/10.1016/j.addbeh.2013.03.003
London, M. (2005). History of Addiction: A UK Perspective. *American Journal on Addictions*, *14*(2), 97–105. http://doi.org/10.1080/10550490590924719
Maloney, E., Degenhardt, L., Darke, S., & Nelson, E. C. (2009). Impulsivity and borderline personality as risk factors for suicide attempts among opioid-dependent individuals. *Psychiatry Res*, *169*(1), 16–21. http://doi.org/10.1016/j.psychres.2008.06.026
Maloney, E., Degenhardt, L., Darke, S., Mattick, R. P., & Nelson, E. (2007). Suicidal behaviour and associated risk factors among opioid-dependent individuals: a case-control study. Addiction, 102(12), 1933–1941. http://doi.org/10.1111/j.1360-0443.2007.01971.x
Marsden, J., Eastwood, B., Ali, R., Burkinshaw, P., Chohan, G., Copello, A., … Day, E. (2014). Development of the Addiction Dimensions for Assessment and Personalised Treatment (ADAPT). Drug Alcohol Depend, 139, 121–131. http://doi.org/10.1016/j.drugalcdep.2014.03.018
Marsden, J., Farrell, M., Bradbury, C., Dale-Perera, A., Eastwood, B., Roxburgh, M., & Taylor, S. (2008). Development of the Treatment Outcomes Profile. *Addiction*, *103*(9), 1450–1460. http://doi.org/10.1111/j.1360-0443.2008.02284.x
Mason, B. J., Kocsis, J. H., Melia, D., Khuri, E. T., Sweeney, J., Wells, A., … Kreek, M. J. (1998). Psychiatric comorbidity in methadone maintained patients. J Addict Dis, 17(3), 75–89. http://doi.org/10.1300/J069v17n03_07
Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., & Hickman, M. (2013). Mortality among people who inject drugs: a systematic review and meta-analysis. Bulletin of the World Health Organization, 91(2), 102–123. http://doi.org/10.2471/BLT.12.108282
Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. In R. P. Mattick (Ed.), Cochrane Database of Systematic Reviews (p. CD002209). Chichester, UK: John Wiley & Sons, Ltd. http://doi.org/10.1002/14651858.CD002209.pub2
Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane Database of Systematic Reviews*, (2), CD002207. http://doi.org/10.1002/14651858.CD002207.pub4

Mattisson, C., Bogren, M., Ojehagen, A., Nordstrom, G., & Horstmann, V. (2011). Mortality in alcohol use disorder in the Lundby Community Cohort--a 50 year follow-up. Drug Alcohol Depend, 118(2–3), 141–147. http://doi.org/10.1016/j.drugalcdep.2011.03.008

McCartney, E. M., & Beard, M. R. (2010). Impact of alcohol on hepatitis C virus replication and interferon signaling. World Journal of Gastroenterology, 16(11), 1337–43. http://doi.org/10.3748/wjg.v16.i11.1337

McCowan, C., Kidd, B., & Fahey, T. (2009). Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. BMJ (Clinical Research Ed.), 338(jun16_4), b2225. http://doi.org/10.1136/bmj.b2225

McGregor, C., Darke, S., Ali, R., & Christie, P. (1998). Experience of non-fatal overdose among heroin users in Adelaide, Australia: circumstances and risk perceptions. Addiction (Abingdon, England), 93(5), 701–11. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9692269

McKay, J. R. (2009). *Treating Substance Use Disorders with Adaptive Continuing Approach*. Washington, DC: Americal Psychological Association.

Menon, K. V, Gores, G. J., & Shah, V. H. (2001). Pathogenesis, diagnosis, and treatment of alcoholic liver disease. Mayo Clin Proc, 76(10), 1021–1029. http://doi.org/10.4065/76.10.1021

Merrall, E. L. C., Bird, S. M., & Hutchinson, S. J. (2013). A record-linkage study of drug-related death and suicide after hospital discharge among drug-treatment clients in Scotland, 1996-2006. Addiction (Abingdon, England), 108(2), 377–84. http://doi.org/10.1111/j.1360-0443.2012.04066.x

Merrall, E. L., Kariminia, A., Binswanger, I. A., Hobbs, M. S., Farrell, M., Marsden, J., … Bird, S. M. (2010). Meta-analysis of drug-related deaths soon after release from prison. Addiction, 105(9), 1545–1554. http://doi.org/10.1111/j.1360-0443.2010.02990.x

Millar, T., Ahmad, M., Richardson, A., Skodbo, S., Donmall, M., & Jones, A. (2012). "The Drug Data Warehouse: Linking data on drug misusers and drug-misusing offenders." *Home Office Research Report*, *63*(March).

Miller, C. L., Kerr, T., Strathdee, S. A., Li, K., & Wood, E. (2007). Factors associated with premature mortality among young injection drug users in Vancouver. Harm Reduction Journal, 4, 1. http://doi.org/10.1186/1477-7517-4-1

Milloy, M.-J. S., Kerr, T., Mathias, R., Zhang, R., Montaner, J. S., Tyndall, M., & Wood, E. (2008). Non-Fatal Overdose Among a Cohort of Active Injection Drug Users Recruited from a Supervised Injection Facility. *The American Journal of Drug and Alcohol Abuse*, *34*(4), 499–509. http://doi.org/10.1080/00952990802122457

Murphy, S. L., Rounsaville, B. J., Eyre, S., Kleber, H. D., Baden, M., Frederick, C., … al., et. (1972). Suicide attempts in treated opiate addicts. *Comprehensive Psychiatry*, *24*(1), 79–89. http://doi.org/10.1016/0010-440X(83)90053-6

Murray, C. J., Lopez, A. D., Bank., W., Murray, C., Lopez, A., Murray, C., … Frenk, J. (1997). Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet (London, England)*, *349*(9061), 1269–76. http://doi.org/10.1016/S0140-6736(96)07493-4

National Drug Treatment Monitoring System. (2013). *Adult Drug Statistics from the National Drug Treatment Monitoring System (NDTMS)*. Retrieved from www.gov.uk/phe. [Date

of retrieval 05January2017]
National Institute for Health and Care Excellence (NICE). (2007). *Methadone and buprenorphine for the Methadone and buprenorphine for the management of opioid dependence management of opioid dependence*. [Date of retrieval 05January2017]
National Treatment Agency for Substance Misuse [NTA]. (2006a). Care planning practice guide. London, UK. [Date of retrieval 05January2017]
National Treatment Agency for Substance Misuse [NTA]. (2006b). Models of care for treatment of adult drug misusers: Update 2006. London, UK. [Date of retrieval 05January2017]
National Treatment Agency for Substance Misuse [NTA]. (2007). Does the combined use of heroin or methadone and other substances increase the risk of overdose? Research Briefing: 27. NTA. [Date of retrieval 05January2017]
National Treatment Agency for Substance Misuse [NTA]. (2009). Towards successful treatment completion: A good practice guide. Effective Treatment Changing Lives. www.nta.nhs.uk: NTA. [Date of retrieval 05January2017]
Neale, J. (2000). Suicidal intent in non-fatal illicit drug overdose. *Addiction (Abingdon, England)*, *95*(1), 85–93. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10723833
Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., & Degenhardt, L. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *The Lancet*, *378*(9791), 571–583. http://doi.org/10.1016/S0140-6736(11)61097-0
Névéol A., Zweigenbaum, P. (2016). Clinical Natural Language Processing in 2015: Leveraging the Variety of Texts of Clinical Interest. *IMIA Yearbook*, 234-239. https://doi.org/10.15265/IY-2016-049
Noble, M., Mclennan, D., Wilkinson, K., & Whitworth, A. (2007). The English Indices of Deprivation 2007. London, UK.
Office For National Statistics (ONS). (2011). *Impact of registration delays on mortality statistics.* [Date of retrieval 17Dec2016]
Office for National Statistics (ONS). (2014). *Quality and Methodology Information*.
Office For National Statistics (ONS). (2015). *Deaths related to drug poisoning in England and Wales, 2014 registrations*. *Statistical Bulletin*. [Date of retrieval 17Dec2016]
Office for National Statistics (ONS). (2016). *Deaths related to drug poisoning in England and Wales: 2015 registrations*. UK. [Date of retrieval 17Dec2016]
Oliver, P., Forrest, R., & Keen, J. (2007). *Study to determine the relationship between blood-heroin/methadone and concomitant drug levels in fatal opioid poisonings*.
Oppenheimer, E., Tobutt, C., Taylor, C., & Andrews, T. (1994). Death and survival in a cohort of heroin addicts at London clinics: a 22 year follow-up study. Addiction, 89, 1299–1308. Retrieved from http://onlinelibrary.wiley.com/store/10.1111/j.1360-0443.1994.tb03309.x/asset/j.1360-0443.1994.tb03309.x.pdf?v=1&t=i5y6f573&s=b5a5b0bcbd83d9d81ae9bb8cb21aa8e6e5d79e09
Page, K., Morris, M. D., Hahn, J. A., Maher, L., & Prins, M. (2013). Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform

comprehensive prevention. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *57 Suppl 2*(Suppl 2), S32-8. http://doi.org/10.1093/cid/cit300

Palmer, R. S., Murphy, M. K., Piselli, A., & Ball, S. A. (2009). Substance user treatment dropout from client and clinician perspectives: a pilot study. Substance Use & Misuse, 44(7), 1021–38. http://doi.org/10.1080/10826080802495237

Patel, R., Jayatilleke, N., Broadbent, M., Chang, C.-K., Foskett, N., Gorrell, G., … Stewart, R. (2015). Negative symptoms in schizophrenia: a study in a large clinical sample of patients using a novel automated method. BMJ Open, 5(9), e007619. http://doi.org/10.1136/bmjopen-2015-007619

Patel, R., Lloyd, T., Jackson, R., Ball, M., Shetty, H., Broadbent, M., … Taylor, M. (2015). Mood instability is a common feature of mental health disorders and is associated with poor clinical outcomes. BMJ Open, 5(5), e007504. http://doi.org/10.1136/bmjopen-2014-007504

Perera, G., Broadbent, M., Callard, F., Chang, C.-K., Downs, J., Dutta, R., … Stewart, R. (2015). Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record derived data resource. *BMJ Open*.

Pierce, M., Bird, S. M., Hickman, M., & Millar, T. (2015). National record linkage study of mortality for a large cohort of opioid users ascertained by drug treatment or criminal justice sources in England, 2005–2009. Drug and Alcohol Dependence, 146, 17–23. http://doi.org/10.1016/j.drugalcdep.2014.09.782

Pierce, M., Bird, S. M., Hickman, M., Marsden, J., Dunn, G., Jones, A., & Millar, T. (2016). Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. *Addiction (Abingdon, England)*, *111*(2), 298–308. http://doi.org/10.1111/add.13193

Powis, B., Strang, J., Griffiths, P., Taylor, C., Williamson, S., Fountain, J., & Gossop, M. (1999). Self-reported overdose among injecting drug users in London: extent and nature of the problem. Addiction (Abingdon, England), 94(4), 471–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10605843

Poynard, T., Bedossa, P., & Opolon, P. (1997). Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet (London, England)*, *349*(9055), 825–32. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9121257

Preti, A., Miotto, P., & De Coppi, M. (2002). Deaths by unintentional illicit drug overdose in Italy, 1984-2000. Drug and Alcohol Dependence, 66(3), 275–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12062462

Prince, M., Stewart, R., & Ford, T. (2003). Practical psychiatric epidemiology. Oxford University Press.

Public Health England. (2013). Estimates of the Prevalence of Opiate Use and/or Crack Cocaine Use, 2011/12: Sweep 8 report. http://www.nta.nhs.uk/uploads/estimates-of-the-prevalence-of-opiate-use-and-or-crack-cocaine-use-2011-12.pdf

Public Health England. (2015). *Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS)*. [Date of retrieval 17Dec2016]

Public Health England. (2015a). *Shooting Up Infections among people who inject drugs in the UK, 2014*. *Public Health England*. [Date of retrieval 17Dec2016]

Public Health England. (2016). *Trends in drug misuse deaths in*. London, UK. [Date of retrieval 17Dec2016]

Quan, V. M., Vongchak, T., Jittiwutikarn, J., Kawichai, S., Srirak, N., Wiboonnatakul, K., … Celentano, D. D. (2007). Predictors of mortality among injecting and non-injecting HIV-negative drug users in northern Thailand. *Addiction*, *102*(3), 441–446. http://doi.org/10.1111/j.1360-0443.2006.01709.x

Ravndal, E., & Amundsen, E. J. (2010). Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study. Drug and Alcohol Dependence, 108(1–2), 65–9. http://doi.org/10.1016/j.drugalcdep.2009.11.008

Ravndal, E., & Vaglum, P. (1998). Psychopathology, Treatment Completion and 5 Years Outcome: A Prospective Study of Drug Abusers. Journal of Substance Abuse Treatment, 15(2), 135–142. http://doi.org/10.1016/S0740-5472(97)00008-1

Recovery Partnership. (2016). *State of Sector Report 2015*. London. [Date of retrieval 16Aug2015]

Roberts, A. (2016). Text Mining Patient Records: Extremely Complicated but Incredibly Rewarding - OpenMinTeD. Retrieved from http://openminted.eu/1129-2/ [Date of retrieval 22November2014]

Robins, L. N. (1993). Vietnam veterans' rapid recovery from heroin addiction: a fluke or normal expectation? *Addiction*, *88*(8), 1041–1054. http://doi.org/10.1111/j.1360-0443.1993.tb02123.x

Robins, L. N., & Regier, D. A. (1991). Psychiatric disorders in America : the epidemiologic catchment area study. Free Press.

Rodriguez-Llera, M. C., Domingo-Salvany, A., Brugal, M. T., Silva, T. C., Sanchez-Niubo, A., & Torrens, M. (2006). Psychiatric comorbidity in young heroin users. *Drug Alcohol Depend*, *84*(1), 48–55. http://doi.org/10.1016/j.drugalcdep.2005.11.025

Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., & Cooke, R. (2005). The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug and Alcohol Review, 24(5), 411–418. http://doi.org/10.1080/09595230500286039

Rossow, I., & Lauritzen, G. (1999). Balancing on the edge of death: suicide attempts and life-threatening overdoses among drug addicts. *Addiction (Abingdon, England)*, *94*(2), 209–19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10396789

Rossow, I., & Lauritzen, G. (2001). Shattered childhood: a key issue in suicidal behavior among drug addicts? *Addiction (Abingdon, England)*, *96*(2), 227–40. http://doi.org/10.1080/09652140020020955

Rounsaville, B. J., Kosten, T. R., Weissman, M. M., & Kleber, H. D. (1986). Prognostic significance of psychopathology in treated opiate addicts. A 2.5-year follow-up study. Arch Gen Psychiatry, 43(8), 739–745.

Rounsaville, B. J., Kranzler, H. R., Ball, S., Tennen, H., Poling, J., & Triffleman, E. (1998). Personality disorders in substance abusers: relation to substance use. The Journal of Nervous and Mental Disease, 186(2), 87–95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9484308

Rounsaville, B. J., Weissman, M. M., Kleber, H., & Wilber, C. (1982). Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch Gen Psychiatry, 39(2), 161–168.

SAMHSA, S. A. and M. H. S. A. (2012). Results from the 2011 National Survey on Drug Use and Health: mental Health Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved from http://www.samhsa.gov/data/NSDUH/2k11MH_FindingsandDetTables/2K11MHFR/NSDUHmhfr2011.htm. [Date of retrieval 22November2014]

Schreiber, W. E., & Giustini, D. M. (2009). Pathology in the era of Web 2.0. Am J Clin Pathol, 132(6), 824–828. http://doi.org/10.1309/ajcpec9fzsb4dedh

Seaman, S. R., Brettle, R. P., & Gore, S. M. (1998). Mortality from overdose among injecting drug users recently released from prison: database linkage study. BMJ (Clinical Research Ed.), 316(7129), 426–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9492665

Serious Organised Crime Agency (SOCA). (2011). *Serious Organised Crime Agency annual report and accounts 2010 to 2011*. Retrieved from https://www.gov.uk/government/publications/serious-organised-crime-agency-annual-report-and-accounts-2010-to-2011. [Date of retrieval 22November2014]

Serious Organised Crime Agency. (2012). *Serious Organised Crime Agency annual report and accounts 2011 to 2012*. Retrieved from https://www.gov.uk/government/publications/serious-organised-crime-agency-annual-report-and-accounts-2011-to-2012. [Date of retrieval 22November2014]

Serious Organised Crime Agency. (2013). *Serious Organised Crime Agency annual report and accounts 2012 to 2013*. Retrieved from https://www.gov.uk/government/publications/serious-organised-crime-agency-annual-report-and-accounts-2012-to-2013. [Date of retrieval 22November2014]

Serious Organised Crime Agency. (2014). *Serious Organised Crime Agency annual report, 2013 to 2014*. Retrieved from https://www.gov.uk/government/publications/serious-organised-crime-agency-annual-report-2013-to-2014. [Date of retrieval 22November2014]

Shah, N. G., Lathrop, S. L., Reichard, R. R., & Landen, M. G. (2008). Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. Addiction, 103(1), 126–136. http://doi.org/10.1111/j.1360-0443.2007.02054.x

Singleton, N. (2003). *Drug-Related Mortality Among Newly Released Offenders*. United Kingdom.

South London and Maudsley NHS Foundation Trust. (2011). Policy for clinical risk assessment and management of harm. London, UK.

Sporer, K. A. (1999). Acute heroin overdose. *Annals of Internal Medicine*, *130*(7), 584–90. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10189329

Stallwitz, A., & Stöver, H. (2007). The impact of substitution treatment in prisons—A literature review. International Journal of Drug Policy, 18(6), 464–474. http://doi.org/10.1016/j.drugpo.2006.11.015

Office for National Statistics (ONS) (2009). Mortality Statistics, Deaths Registered in 2008. [Date of retrieval 22November2014]

Stebnacka, M., Leifman, A., & Romelsjo, A. (2009). Mortality and cause of death among 1705 illicit drug users: A 37 year follow up. *Drug and Alcohol Review*, *29*(1), 21–27. http://doi.org/10.1111/j.1465-3362.2009.00075.x

Stewart, R., Soremekun, M., Perera, G., Broadbent, M., Callard, F., Denis, M., … Lovestone, S. (2009). The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. *BMC Psychiatry*, *9*, 51. http://doi.org/10.1186/1471-244x-9-51

Story, A., Murad, S., Roberts, W., Verheyen, M., Hayward, A. C., & London Tuberculosis Nurses Network. (2007). Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax*, *62*(8), 667–71. http://doi.org/10.1136/thx.2006.065409

Strader, D. B. (2005). Coinfection with HIV and Hepatitis C Virus in Injection Drug Users and Minority Populations. *Clinical Infectious Diseases*, *41*(Supplement 1), S7–S13. http://doi.org/10.1086/429489

Strang, J. (1990). Lessons from an English opium eater: Thomas De Quincey reconsidered. *The International Journal of the Addictions*, *25*(12), 1455–65.

Strang, J. (2015). Death matters: understanding heroin/opiate overdose risk and testing potential to prevent deaths. Addiction, 110, 27–35. http://doi.org/10.1111/add.12904

Strang, J., Babor, T., Caulkins, J., Fischer, B., Foxcroft, D., Humphreys, K., … Liu, L.-M. (2012). Drug policy and the public good: evidence for effective interventions. *Lancet (London, England)*, *379*(9810), 71–83. http://doi.org/10.1016/S0140-6736(11)61674-7

Strang, J., Drummond, C., Mcneill, A., Lader, M., & Marsden, J. (2014). Annual Report of the Chief Medical Officer 2013, Public Mental Health Priorities: Investing in the Evidence Key statistics. London.

Strang, J., Manning, V., Mayet, S., Titherington, E., Offor, L., Semmler, C., & Williams, A. (2008). Family carers and the prevention of heroin overdose deaths: Unmet training need and overlooked intervention opportunity of resuscitation training and supply of naloxone. http://doi.org/10.1080/09687630701731205

Strang, J., McCambridge, J., Best, D., Beswick, T., Bearn, J., Rees, S., & Gossop, M. (2003). Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *BMJ (Clinical Research Ed.)*, *326*(7396), 959–60. http://doi.org/10.1136/bmj.326.7396.959

Su, Y.-P., Chang, C.-K., Hayes, R. D., Perera, G., Broadbent, M., To, D., … Stewart, R. (2014). Mini-mental state examination as a predictor of mortality among older people referred to secondary mental healthcare. PloS One, 9(9), e105312. http://doi.org/10.1371/journal.pone.0105312

Sultana, J., Chang, C. K., Hayes, R. D., Broadbent, M., Stewart, R., Corbett, A., & Ballard, C. (2014). Associations between risk of mortality and atypical antipsychotic use in vascular dementia: a clinical cohort study. *International Journal of Geriatric Psychiatry*, *29*(12), 1249–54. http://doi.org/10.1002/gps.4101

Swift, W., Maher, L., & Sunjic, S. (1999). Transitions between routes of heroin administration: a study of Caucasian and Indochinese heroin users in south-western Sydney, Australia. *Addiction*, *94*(1), 71–82

Tagliaro, F., Battisti, Z. De, Smith, F. P., & Marigo, M. (1998). Death from heroin overdose:

findings from hair analysis. The Lancet, 351(9120), 1923–1925. http://doi.org/10.1016/S0140-6736(97)10101-5

Taylor, A., Munro, A., Allen, E., Dunleavy, K., Cameron, S., Miller, L., & Hickman, M. (2013). Low incidence of hepatitis C virus among prisoners in Scotland. Addiction, 108(7), 1296–1304. http://doi.org/10.1111/add.12107

Teesson, M., Havard, A., Fairbairn, S., Ross, J., Lynskey, M., & Darke, S. (2005). Depression among entrants to treatment for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence, correlates and treatment seeking. *Drug and Alcohol Dependence*, *78*(3), 309–315. http://doi.org/10.1016/j.drugalcdep.2004.12.001

Tsirigotis, K., Gruszczynski, W., & Tsirigotis, M. (2011). Gender differentiation in methods of suicide attempts. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *17*(8), PH65-70.

UNAIDS (The Joint United Nations Programme on HIV/AIDS). (2004). *2004 Report on the global AIDS epidemic*. Geneva, Switzerland.

United Nations Office on Drugs and Crime (UNODC). (2015). World Drug Report 2015. Vienna.

United Nations Office on Drug and Crime (UNODC). (2012). *World Drug Report 2012*. Vienna, Austria.

Vingoe, L., Welch, S., Farrell, M., Strang, J., Vingoe, L., Welch, S., … Strang, J. (2009). Heroin overdose among a treatment sample of injecting drug misusers: accident or suicidal behaviour? In Journal of Substance Use (Vol. 4).

Wadland, W. C., & Ferenchick, G. S. (2004). Medical comorbidity in addictive disorders. Psychiatric Clinics of North America, 27(4), 675–687. http://doi.org/10.1016/j.psc.2004.06.006

Walsh, S. L., June, H. L., Schuh, K. J., Preston, K. L., Bigelow, G. E., & Stitzer, M. L. (1995). Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology*, *119*(3), 268–276. http://doi.org/10.1007/BF02246290

Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E. J., & Bigelow, G. E. (1994). Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clinical Pharmacology and Therapeutics, 55(5), 569–80.

Wand, T. (2012). Investigating the Evidence for the Effectiveness of Risk Assessment in Mental Health Care. Issues in Mental Health Nursing, 33(1), 2–7. http://doi.org/10.3109/01612840.2011.616984

Warner-Smith, M., Darke, S., & Day, C. (2002). Morbidity associated with non-fatal heroin overdose. *Addiction (Abingdon, England)*, *97*(8), 963–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12144598

Warner-Smith, M., Darke, S., Lynskey, M., & Hall, W. (2001). Heroin overdose: causes and consequences. *Addiction (Abingdon, England)*, *96*(8), 1113–25. http://doi.org/10.1080/09652140120060716

Weaver, T., Madden, P., Charles, V., Stimson, G., Renton, A., Tyrer, P., … Ford, C. (2003). Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. *Br J Psychiatry*, *183*, 304–313.

White, S. R., Bird, S. M., Merrall, E. L. C., & Hutchinson, S. J. (2015). Drugs-Related Death

Soon after Hospital-Discharge among Drug Treatment Clients in Scotland: Record Linkage, Validation, and Investigation of Risk-Factors. PLOS ONE, 10(11), e0141073. http://doi.org/10.1371/journal.pone.0141073

Wiessing, L., Ferri, M., Grady, B., Kantzanou, M., Sperle, I., Cullen, K. J., … Hickman, M. (2014). Hepatitis C Virus Infection Epidemiology among People Who Inject Drugs in Europe: A Systematic Review of Data for Scaling Up Treatment and Prevention. *PLoS ONE*, *9*(7), e103345. http://doi.org/10.1371/journal.pone.0103345

Wilcox, H. C., Conner, K. R., & Caine, E. D. (2004). Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. *Drug and Alcohol Dependence*, *76*, S11–S19. http://doi.org/10.1016/j.drugalcdep.2004.08.003

Williams, A. V., Marsden, J., & Strang, J. (2014). Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction, 109(2), 250–259. http://doi.org/10.1111/add.12360

Wines Jr., J. D., Saitz, R., Horton, N. J., Lloyd-Travaglini, C., & Samet, J. H. (2007). Overdose after detoxification: A prospective study☆. *Drug and Alcohol Dependence*, *89*(2–3), 161–169. http://doi.org/10.1016/j.drugalcdep.2006.12.019

Wing, J. K., Beevor, A. S., Curtis, R. H., Park, S. B., Hadden, S., & Burns, A. (1998). Health of the Nation Outcome Scales (HoNOS). Research and development. *The British Journal of Psychiatry : The Journal of Mental Science*, *172*, 11–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9534825

World Health Organisation (WHO). (2013). Mortality among people who inject drugs: a systematic review and meta-analysis. Bulletin of the World Health Organization, 91(2), 102–23. http://doi.org/10.2471/BLT.12.108282

World Health Organisation (WHO). (2014).Information sheet on opioid overdose. Retrieved from http://www.who.int/substance_abuse/information-sheet/en/ [Date of retrieval 22November2014]

World Health Organization. (1993). The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva.

Wu, C.-Y., Chang, C.-K., Hayes, R. D., Broadbent, M., Hotopf, M., & Stewart, R. (2012). Clinical risk assessment rating and all-cause mortality in secondary mental healthcare: the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) Case Register. Psychological Medicine, 42, 1581–1590. http://doi.org/10.1017/S0033291711002698

Wu, C.-Y., Chang, C.-K., Robson, D., Jackson, R., Chen, S.-J., Hayes, R. D., & Stewart, R. (2013). Evaluation of smoking status identification using electronic health records and open-text information in a large mental health case register. PloS One, 8(9), e74262. http://doi.org/10.1371/journal.pone.0074262

Yin, L., Qin, G., Ruan, Y., Qian, H.-Z., Hao, C., Xie, L., … Shao, Y. (2007). Nonfatal Overdose Among Heroin Users in Southwestern China. *The American Journal of Drug and Alcohol Abuse*, *33*(4), 505–516. http://doi.org/10.1080/00952990701407223

Zanis, D. A., & Woody, G. E. (1998). One-year mortality rates following methadone treatment discharge. *Drug and Alcohol Dependence*, *52*(3), 257–60.

APPENDICES

(i) **Submitted manuscript**: Excess overdose mortality immediately after cessation of opioid substitute therapy and following transfer of patients and their care: findings from analysis of integration of deaths data with catchment area healthcare data on a sample of opioid use disorder patients.

(ii) **Published report**: Identifying mortality risks in patients with opioid use disorder using brief screening assessment: Secondary mental health clinical records analysis. published report.

(iii) **Published report**: Double trouble: Psychiatric comorbidity and opioid addiction – all-cause and cause-specific mortality.

(iv) **Published abstract**: Psychiatric comorbidity and excess all-cause and cause-specific mortality in opioid addicts.

(v) Example of data extraction (used for analysis in Chapter 5)

(vi) Treatment Outcome Profile (TOP) (Marsden et al., 2008)

(vii) KCL ethics approval for technical appraisal - qualitative study

(i) Submitted manuscript (Chapter 6)

Addiction

Excess overdose mortality immediately after cessation of opioid substitute therapy and following transfer of patients and their care: findings from analysis of integration of deaths data with catchment area healthcare data on a sample of opioid use disorder patients.

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SUBSTANCE:	opiates
METHOD:	clinical observations
FIELD OF STUDY:	epidemiology
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Excess overdose mortality immediately after cessation of opioid substitute therapy and following transfer of patients and their care: findings from analysis of integration of deaths data with catchment area healthcare data on a sample of opioid use disorder patients.

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RH and RS have received research funding from Roche, Pfizer, J&J, Janssen and Lundbeck and In Silico Biosciences. JS has conducted a variety of research studies of addictive disorders and treatments and through the university, has provided consultancy to pharmaceutical companies about new treatments for opioid addiction, including (last 3 years) Martindale, MundiPharma and Braeburn for which his employer has received remuneration and specific research grant income. None was the subject of study in this work. For further description see:
www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. KMB and ED have no conflict of interest to declare.

ABSTRACT: (300)

Aims: To investigate clustering of deaths in the period immediately after transfer of patients and their care and after the end of opioid substitution therapy (OST) in opioid dependent individuals in specialist addiction treatment.

Design, Setting and Participants: Mortality data were identified within a sample of 5,445 patients with opioid use disorder who had received OST treatment between 1st April 2008 and 31st December 2013. We investigated the circumstances and distribution of the 332 deaths identified within the observation window.

Measurements: Mortality incidence rates after the end of treatment/transfer for overdose mortality.

Findings: We have identified higher concentrations of overdose deaths in the first 28 days after a planned end of OST treatment and within 28 days after a transfer of patient between services, even when continuation of OST treatment had been arranged. 18 out of 32 (56%) patients died within 180 days of planned treatment cessation, of which 5 died in the first 2 weeks and a further 4 died in the first month post-termination of OST. Of the 47 individuals who died from overdose after having been transferred between services, 20 (43%) died within 180 days of this transfer, of which 9 died in the first 2 weeks and a further 5 died in the first month post-transfer. These results translate into an overdose mortality rate of 77.2 per 1000 person-days within 28 days post-OST cessation/transfer, compared with a rate of 1.9 per 1000 person-days for overdoses after the first month of treatment cessation/transfer (rate ratio=41.4; 25.1-66.1 95% CI; p <0.0001).

Conclusions: High clustering of fatal overdoses in the early post-OST period was observed. We also found a substantially higher concentration of deaths in the period immediately following transfer of patients to a different treatment care-provider. This excess mortality is pronounced in the first month post-transfer, and especially so in the first fortnight. Further research is urgently required.

INTRODUCTION

Research has shown consistently that opioid substitution therapy (OST) is associated with reduced mortality (e.g. 2,3). More recently, it has also been identified that there is a short-lived substantial excess mortality after termination of OST where, in a national primary care cohort, the risk of death has been found to increase eight-fold in the month immediately after the end of OST (4). Several other studies have reported similar findings (5,6), but none has examined interruptions to continuity of care, such as transfers of patients to alternative services or care-providers.

We are currently investigating mortality patterns amongst patients with opioid use disorder who have received OST treatment using data from a large secondary mental health care provider (7,8). Within this work, we have examined factors associated with clustering of deaths.

METHODS

Study Setting

The South London and Maudsley NHS Foundation Trust (SLaM) is one of the largest secondary mental healthcare services in Europe, providing addiction services to a catchment population of approximately 1.36 million residents across seven ethnically and socially diverse, high population density boroughs of south-east London (7). In 2008, the Clinical Record Interactive Search (CRIS) was developed, which accesses patients' electronic health records in a de-identified format, allowing researchers to search and retrieve complete case records for analysis. There are currently more than 260,000 patients represented on the system. CRIS is approved as a dataset for secondary analysis by Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5), and its protocol is described in detail elsewhere (7,8).

Study Sample

The study sample comprised SLaM patients diagnosed with primary or secondary opioid use disorder (OUD; International Classification of Diseases [ICD-10] [9]: F11) an ICD-10 F11 primary or secondary opioid use disorder (OUD) between 1st April 2008 and 31st December 2013 who died within the same observation period.

Every death in the UK is reported to the Office for National Statistics (ONS) General Records Office, which is then conveyed to the NHS Care Records Service and available to all NHS organisations; and consequently in CRIS. This identifies deaths within the observation period, for both current and previous SLaM patients. The full procedure for identifying and confirming SLaM patient deaths has been described elsewhere (10). In addition, a linkage to data specifically derived from death certificates allowed us to establish the recorded underlying cause of each death in those where this information was available.

Diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using natural language processing (NLP). The NLP application for 'diagnosis' extracts any text strings associated with a diagnosis statement in order to supplement the structured fields, the performance of which has been reported elsewhere. (7)

Measures and Calculations

The present study investigated potential clustering of deaths after a clinically planned termination of OST and after a transfer of patient and their care to another service or care provider, with arrangement for continuation of OST. The main characteristic of interest in this study was the timing of death, specifically overdose deaths, in OUD patients who were prescribed OST treatment. Incidence rates were calculated and Kaplan-Meier curves used to visualise the results.

Treatment episodes

Using CRIS, we extracted de-identified individual records on all patients with an OUD who died between 1st April 2008 to 31st December 2013. Searching backwards from each death date, we looked for the start and end dates of the most recent OST treatment episode. This information was primarily derived from treatment care plan notes, with each OST treatment episode starting with the date of the first prescription for substitute opioids relating to most recent treatment episode and ended with the expiry of their last prescription. The name of the last prescribed OST medication was also noted.

In all cases, a search through discharge notes and free-text fields, including event notes and correspondence, was also conducted manually for validation purposes and to supplement data not available in the structured fields. Particular attention was given to treatment episodes with a gap of less than 28 days between the end of one episode and the start date of the next. In such cases, examination of event and discharge notes was particularly useful, as it allowed us to establish whether a patient genuinely stopped and restarted their treatment in a four-week period. We adopted the '28-day rule' from Cornish and colleagues (4).

Categorising reasons for end of treatment

Reasons for cessation of OST treatment were extracted from patients' treatment care plans, in discharge notes and other free-text fields. By cross-examining these sources, we categorised reasons for end of treatment into the following: 1. 'Planned end of treatment' (patients with a clinically planned discharge following cessation of OST); 2. 'Transfer' (patients who were transferred to another service or care provider who would

then take over patients' care including OST prescribing); 3. 'Dropout' (patients with a clinically unplanned OST cessation, such as non-compliance, failure to attend key-working sessions and/or failure to collect prescribed OST medications); and 4. 'Died in treatment' (if death occurred during an OST treatment episode). Types of transfer were also noted.

RESULTS

Sample characteristics

The total number of patients with primary or secondary ICD10 F11 OUD diagnosis within the observation window was 5335, with 385 deaths identified in this sample. Of the 385 individuals who died, 53 (14%) were never prescribed OST within SLaM and/or their records contained no information with regard to their treatment history, and were therefore excluded from analysis. A further 116 (35%) of the remaining 332 patients died whilst still in OST treatment in SLaM and hence were not considered further in this analysis of deaths post-OST treatment and post-transfer.

The remaining sample of 216 deaths comprised 66 patients with a planned termination of OST treatment, 109 who were transferred to another service or care-provider, and 41 who dropped out of OST treatment.

As presented in Table 1, most patients were male, with mean age of 45 years at the time of their death. The median duration of patients' last OST treatment episode was just below 8 months (235.5 days, inter-quartile range 52-560 days) and the median interval between end of treatment/transfer and death was almost 1 year (349 days, inter-quartile range 62-800 days). Most destinations for transfers between services were primary care, followed by independent/third-sector drug treatment providers, transfer to alternative (usually out of area) community and drug alcohol services, and to general hospitals.

Mortality rates

Under the assumption that the number of patients under treatment remain constant throughout the observation window, we observe what appears to be a higher concentration of all-cause deaths within a month after a planned end of OST treatment and also high concentrations of deaths in the first month after a transfer between services, even when continuation of OST treatment was arranged. There were 66 individuals who died after a planned termination of OST treatment and 109 who died after a transfer between services. Of the 66 individuals who died after a planned termination of OST treatment, 27 (41%) died within 180 days of treatment cessation, with 12 of those being within the first 28 days and 7 within the first fortnight post-termination. Of the 109 who

died after transfer between services, 43 (39%) died within 180 days of this transfer, with 26 dying in the first 28 days and 17 within the first fortnight post-transfer. Similarly, of the 41 who died after having dropped out of treatment, 12 (29%) died within 180 days of this transfer, with 4 of these being within the first fortnight post-drop-out (details not shown in tables).

Our primary interest was in deaths caused by a fatal overdose. We were able to ascertain the cause of death in 96% of patients (208 out of 216), summarised in Table 2. Overdose fatalities were the most common (49%) followed by hepatic-related deaths (14%). To establish whether transfer of care and termination of OST treatment were associated with increased risk of overdose, we restricted our further analysis to fatal overdoses only. Of the 103 individuals who died of overdose, 47 were in the post-transfer subgroup and 32 occurred after a planned end of OST, and with high clustering of overdoses occurring in both subgroups.

More specifically, 20 out of 47 (43%) of the post-transfer overdoses occurred within 180 days, of which 9 died in the first 2 weeks and a further 5 died in the first month. Similarly, 18 out of 32 (56%) of overdoses occurred within 180 days of planned OST cessation, of which 5 died in the first 2 weeks and a further 4 died in the first month. Twenty-four overdoses occurred in the drop-out group, and with 5 occurring within 180 days but none were recorded within the first fortnight. Figures 1 and 2 show distribution of overdose deaths within 180 days post-transfer with continuation of OST treatment and post-treatment with planned cessation of OST, respectively.

Combining the three reasons for OST treatment end (transfer, planned discharge and drop-out), the total follow-up -time was 42716 person-days, with 311 person-days in the group who fatally overdosed in the first 28 days after post-OST cessation/transfer; and with a rate of 77.2 deaths per 1000 person days compared with a rate of 1.9 deaths per 1000 person days in the group who died of overdose after the first month of treatment cessation/transfer. The rate ratio comparing the two groups was 41.4 (25.1-66.1 95% CI; p <0.0001). Figures 1 shows the survival probabilities for time since the end of treatment/transfer and overdose mortality for total follow-up time. Figure 2 displays the survival probabilities for time since end of treatment/transfer and overdose mortality within 180 days after end of treatment, stratified by reasons for end of treatment.

DISCUSSION

This study examined circumstances surrounding the deaths of patients with a diagnosis of opioid use disorder who had received OST treatment in SLaM within a near five-year observation period. In addition to substantial clustering of deaths in the early post-OST period as reported by others (4–6), there was also a substantial excess mortality, and especially overdose mortality, in the period immediately following transfer of the patient and their care to a different treatment care-provider, with this excess mortality pronounced in the first month post-transfer.

Increased risk of death immediately after dropout from treatment may not be surprising (13) and overdose risk post-termination of OST treatment is already recognised (4,6). However, our finding of a marked excess of overdose deaths in the period immediately after transfers of patients and their care despite continuation of OST treatment is new and unexpected. Large 'transferred' subgroups included patients experiencing transitions from secondary to primary care or to large independent care-provider organisations who had secured new NHS contracts after the introduction of competitive tendering procedures (12). If the purpose of such re-organisation is to achieve greater effectiveness and more cost-effective use of resources, then it might have been expected that we would find successful transfer of patients and their treatments, patient stability, and stable or lowered risk of mortality (13); however our analysis instead indicated a high number of fatal overdoses particularity in the first month post-transfer. This needs deeper and wider exploration.

Little is known about the de-stabilisation that may accompany changes to service delivery. The present data did not allow us to ascertain what happened to patients after a transfer. Consequently, we were not able to establish whether any failures had occurred during the period of transition itself, or whether any de-stabilisation occurred after a successful transition to the new care provider.

This study urgently needs fuller exploration and replication. Before any potential explanations are discussed with regard to the mechanisms behind excess deaths post-transfer with continuation of OST, further investigations should focus on exploring these findings using extended data and inferential statistics, as well as service-user

consultations. Although the current analyses were limited to crude associations, these findings provide important insights into practice, the impact of service organisation (including service re-organisational changes) and the associated risks of overdose deaths.

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REFERENCES

1. Office For National Statistics (ONS). Deaths related to drug poisoning in England and Wales, 2014 registrations. Statistical Bulletin. 2015.
2. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. Subst Use Misuse [Internet]. 1996 Jan [cited 2016 Mar 4];31(2):177–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8834006
3. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane database Syst Rev [Internet]. 2003 Jan [cited 2016 Apr 1];(3):CD002208. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12917925
4. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ [Internet]. 2010 Jan 26 [cited 2016 Apr 1];341(oct26_2):c5475. Available from: http://www.bmj.com/content/341/bmj.c5475
5. Davoli M, Bargagli AM, Perucci CA, Schifano P, Belleudi V, Hickman M, et al. Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. Addiction. 2007/11/23 ed. 2007;102(12):1954–9.
6. Strang J, McCambridge J, Best D, Beswick T, Bearn J, Rees S, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. BMJ [Internet]. 2003 May 3 [cited 2016 Apr 5];326(7396):959–60. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=153851&tool=pmcentrez&rendertype=abstract
7. Perera G, Broadbent M, Callard F, Chang C-K, Downs J, Dutta R, et al. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. BMJ Open [Internet]. 2016 Jan 1 [cited 2016 Mar 16];6(3):e008721. Available from: http://bmjopen.bmj.com/content/6/3/e008721.abstract
8. Stewart R, Soremekun M, Perera G, Broadbent M, Callard F, Denis M, et al. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry. 2009/08/14 ed. 2009;9:51.
9. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva; 1993.
10. Chang CK, Hayes RD, Broadbent M, Fernandes AC, Lee W, Hotopf M, et al. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry. 2010/10/06 ed. 2010;10:77.
11. Zanis DA, Woody GE. One-year mortality rates following methadone treatment discharge. Drug Alcohol Depend. 1998;52(3):257–60.
12. Department of Health [DOH]. Changes to the National Health Service (Procurement, Patient Choice and Competition) Regulations 2013. London, UK; 2013.
13. Darke S, Williamson A, Ross J, Teesson M. Non-fatal heroin overdose, treatment exposure and client characteristics: findings from the Australian treatment outcome study (ATOS). Drug Alcohol Rev. 2005/11/22 ed. 2005;24(5):425–32.
14. Merrall EL, Kariminia A, Binswanger IA, Hobbs MS, Farrell M, Marsden J, et al. Meta-analysis of drug-related deaths soon after release from prison. Addiction. 2010/06/29 ed. 2010;105(9):1545–54.
15. Farrell M, Marsden J. Acute risk of drug-related death among newly released prisoners in England and Wales. Addiction [Internet]. 2008 Feb [cited 2016 Apr 14];103(2):251–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18199304

TABLES AND FIGURES

Table 1 Sample characteristics

	N (%)
Total Study Sample	**216**
Males	151 (69.9)
Age	
>= 29	17 (7.9)
30-39	55 (25.5)
40-49	73 (33.8)
50-59	49 (22.7)
60+	22 (10.1)
Planned OST end	66 (30.6)
Drop-Outs	41 (19)
Transfer between services	**109 (50.5)**
Transfer to primary care	42 (38.5)
Transfer to independent/third-party sector	21 (19.3)
Transfer to alternative community drug treatment service	16 (14.7)
Transfer to general hospital	14 (12.8)
Transfer to prison	5 (4.6)
Other transfers	11 (10.9)
Last prescribed medication	
Methadone	179 (82.9)
Buprenorphine	31 (14.3)
Other (diamorphine, Suboxone, morphine)	6 (2.8)
Last treatment episode duration	
One month or less	37 (17.1)
Between one month and six months	59 (27.3)
Between six months and one year	43 (19.9)
More than one year	77 (35.6)

Table 2 Underlying causes of death (n=208 / 216)

Underlying cause of death	Total (%)	Males	Females
Overdose	103 (49.5)	71 (68.9)	32 (31.1)
Liver disease	30 (14.4)	22 (73.3)	8 (26.7)
Infectious disease	12 (5.8)	9 (75)	3 (25)
Pneumonia and other pulmonary	15 (7.2)	11 (73.3)	4 (26.7)
Other natural cause	30 (14.4)	17 (56.7)	13 (43.3)
Other unnatural cause	15 (7.2)	14 (93.3)	1 (6.7)
Unspecified	3 (1.4)	2 (66.7)	1 (33.3)

Fig. 1 Kaplan Meier survival curves for time since SLaM treatment cessation/transfer (in days) for overdose deaths.

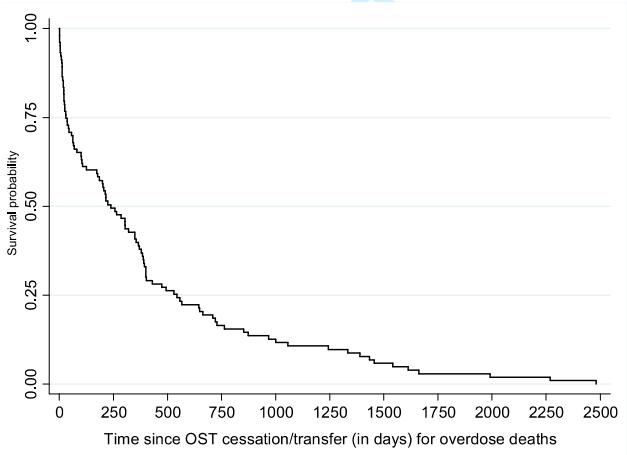
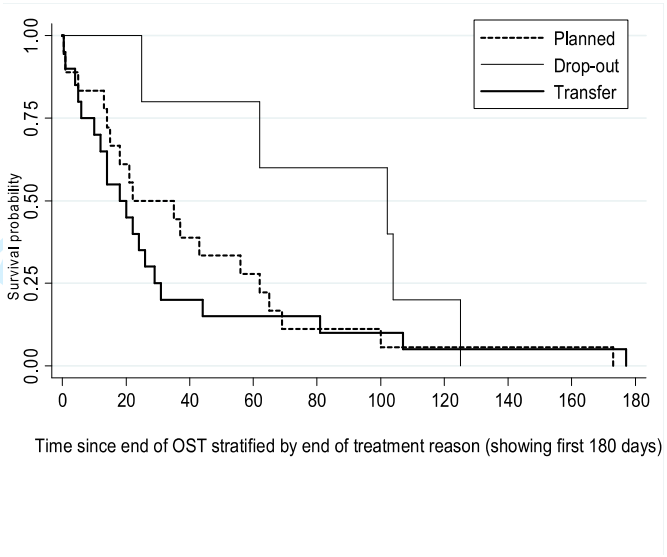


Fig. 2 Kaplan Meier survival curves for time since SLaM treatment cessation/transfer (in days) for overdose deaths, stratified by reasons for end of treatment or transfer (showing first 180 days).



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Full length article

Identifying mortality risks in patients with opioid use disorder using brief screening assessment: Secondary mental health clinical records analysis

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ABSTRACT

Background: Risk assessments are widely used, but their ability to predict outcomes in opioid use disorder (OUD) treatment remains unclear. Therefore, the aim was to investigate if addiction-specific brief risk screening is effective in identifying high mortality risk groups and if subsequent clinical actions following risk assessment impacts on mortality levels.
Methods: Opioid use disorder (OUD) patients were identified in the South London and Maudsley Case Register. Deaths were identified through database linkage to the national mortality dataset. Cox and competing-risk regression were used to model associations between brief risk assessment domains and all-cause and overdose mortality in 4488 OUD patients, with up-to 6-year follow-up time where 227 deaths were registered. Data were stratified by admission to general mental health services.
Results: All-cause mortality was significantly associated with unsafe injecting (HR 1.53, 95% CI 1.10–2.11) and clinically appraised likelihood of accidental overdose (HR 1.48, 95% CI 1.00–2.19). Overdose-mortality was significantly associated with unsafe injecting (SHR 2.52, 95% CI 1.11–5.70) and clinically appraised suicidality (SHR 2.89, 95% CI 1.38–6.03). Suicidality was associated with a twofold increase in mortality risk among OUD patients who were not admitted to mental health services within 2 months of their risk assessment (HR 2.03, 95% CI 1.67–3.24).
Conclusions: Diagnosis-specific brief risk screening can identify OUD patient subgroups at increased risk of all-cause and overdose mortality. OUD patients, where suicidality is evident, who are not admitted into services are particularly vulnerable.

1. Introduction

People dependent on heroin or other opioids are up to 14 times more likely to die than their peers (Darke and Ross, 2002). Worldwide, an estimated 69,000 people die from opioid overdose (accidental or deliberate) each year (World Health Organisation (WHO), 2014). In England and Wales, more than 1700 deaths registered in 2014 (53% of all deaths from drug poisoning) involved an opiate drug (Office For National Statistics (ONS), 2015). Assessing and managing risks is a paramount element of care planning and treatment provision to people with drug dependence, particularly in opioid dependence (Department of Health (DOH), 2007). Assessment of risks within the addictions services should be substance misuse specific, prioritizing directly related risks such as overdose, poly-drug use, suicide and/or unsafe injecting practices (National Treatment Agency for Substance Misuse (NTA), 2006a,b).

The effectiveness of risk assessment tools in predicting mortality in mental healthcare is unclear. Wand, 2012 reported inability to conduct a systematic review due to paucity of studies evaluating the effectiveness of risk assessments, and found little evidence to conclude whether risk assessments are effective in relation to self-harm or suicide reduction. Studies attempting to identify individuals who are likely to die by suicide have been largely unsuccessful primarily due to its low prevalence, even within high-risk

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groups (Harriss and Hawton, 2005; Kapur, 2005). A recent study of people receiving secondary mental healthcare reported that the level of clinically appraised risk of self-neglect (but not suicide or violence) predicted all-cause mortality, but the study did not stratify results by diagnosis or examined cause-specific mortality (Wu et al., 2012). Given the differences in aetiology, symptoms, care provision and risk factors between mental health diagnostic groups, it is important to investigate these separately as advised by the NTA (2006a). Therefore, the aim of the current study was to determine if addiction-specific brief risk assessment completed for opioid use disorder patients is effective in predicting risks of all-cause and overdose mortality; to investigate mortality levels in patients clinically appraised as displaying suicidality, increased likelihood of accidental overdose and unsafe injecting practices; and to determine if associations between clinically appraised risks and mortality differs depending on subsequent clinical actions such as admission to secondary mental health services and the type of opioid substitution therapy (OST) prescribed.

2. Methods

2.1. Study setting

South London and Maudsley NHS Foundation Trust (SLaM) is one of the largest secondary mental healthcare services in Europe, currently providing comprehensive mental healthcare and addiction service to a catchment population of approximately 1.2 million residents across seven ethnically and socially diverse, high population density boroughs of south London. SLaM addiction services have used electronic health records (EHRs) since April 2008. In the same year, at the SLaM NIHR Biomedical Research Centre for Mental Health, the Clinical Record Interactive Search (CRIS) was developed. CRIS uses EHRs in a de-identified format, allowing researchers to search and retrieve complete case records for analytical purposes. There are currently more than 260,000 patients represented on the system. CRIS was approved as a dataset for secondary analysis by Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5), and its protocol is described in detail elsewhere (Perera et al., 2016; Stewart et al., 2009).

2.2. Inclusion criteria

Diagnoses in SLaM are coded in accordance with the 10th edition of the World Health Organization International Classification of Diseases (ICD-10; WHO, 1993). This study cohort comprised SLaM patients who were diagnosed with an ICD-10 F11 primary or secondary opioid use disorder (OUD) between 1st April, 2008 to 31st March, 2014 (inclusive), and who had at least one item completed on the Brief Risk Scale Assessment—Addiction (BRSA-A) during the observation period. Diagnoses were derived from their designated SLAM EHR structured fields and from free-text fields using Natural Language Processing (NLP). The NLP application for 'diagnosis' sought to extract any text strings associated with a diagnosis statement in order to supplement the existing structured fields. The performance of the 'diagnosis' NLP application was evaluated formally elsewhere (Sultana et al., 2014). In the SLaM case register, OUD is the second most frequently diagnosed substance use disorder after alcohol use dependence (Hayes et al., 2011).

2.3. Main outcome measures

2.3.1. All-cause mortality. The main outcome in this study was all-cause mortality in individuals with primary or secondary diagnosis of OUD, within the period 1st April, 2008 to 31st March, 2014. Every death in the UK is reported to the Office for National Statistics General Records Office, which is then conveyed to the NHS Care Records Service and available to all NHS organisations. Majority of deaths are registered with ONS within five days and SLaM mortality updates are performed on a monthly basis. This allowed us to establish deaths within the observation period, for both active and inactive SLaM patients. The full procedure for identifying and confirming SLaM patient deaths has been described elsewhere (Chang et al., 2010).

2.3.2. Cause-specific mortality. Additionally, 68.7% of all those who died had death certificate information. This information allowed us to establish cause-specific mortality, and more specifically coding for overdose mortality. Fatal overdoses included a combination of both intentional (i.e., suicide) and unintentional (i.e., drug poisoning) overdose deaths, with ICD-10 codes X409-X450, Y120, Y125 and F119 sub-classified as such. The relationship between heroin overdose and suicide is problematic due to ambiguous circumstantial information and unclear intent (Cantor et al., 2001), therefore for these analyses, we grouped suicide by overdose and fatal drug poisonings into one group. The cause of death information is based on a static ONS-CRIS data linkage and is more likely to reflect a proportion of delayed as well as recent occurrences of deaths within the ONS (ONS, 2011), resulting in the 31% missing causes of death in our cohort.

2.4. Exposures

The main exposures of interest in this study were patients' risks of suicidality, likelihood of overdose and injecting practices. These three risk domains were recorded using the Addiction Brief Risk Scale Assessment (BRSA-A) (described below) in patients with OUD

In addition to the main exposures of interest, a number of other covariates were considered as potential confounders. Patients' risks associated with violence, health, social variables, and service use were also recorded on the BRSA-A. Ethnicity and gender are routinely recorded on SLaM electronic patient records in their designated fields. Age was calculated on the date on which individuals received their first BRSA-A assessment within the observation period. Ethnic group classifications were condensed to "White British", "Other White background", "African, Caribbean and other black background", and "Mixed, unknown and other". Area-level deprivation was established by linking the patient's residential postcode to the UK Census data projected for 2007 in lower super output area units. The full procedure for measuring level of deprivation is described elsewhere (Hayes et al., 2012). Homelessness variable was established by merging information from area-level deprivation and homelessness/unstable housing item on the BRSA-A scale. Information on patient admissions to a SLaM secondary mental health service in the two-month period after BRSA-A assessment was also extracted. This information included general admissions to SLaM, and information on prescription of opioid substitute treatment (OST) medication (i.e., buprenorphine, methadone, Suboxone [buprenorphine/naloxone]) in the 2-month period after BRSA-A completion. Information extracted included both inpatient and outpatient community service admissions/prescriptions in a 60-day (two months) observation period after the BRSA-A completion.

2.5. Risk assessment instrument

The BRSA-A is a compulsory target for the addictions clinical team on all active cases. This risk measure was developed by SLaM clinicians to encourage identification and formal recording of risk areas specific to substance misuse patients; these are then used in their care planning. BRSA-A should be completed for each service user at the point of referral, as part of the service user's initial assessment when he/she first comes into contact with SLaM ser-

Table 1
Cohort characteristics.

Variables	Number of individuals	Number of deaths (% per row)
Total	4488	227 (5.1)
BRSA-A items and domains		
Suicide		
Suicide attempt history	1279	91 (7.1)
Suicide ideations	306	13 (4.2)
Carer concern	205	17 (8.3)
Major mental illness	1225	75 (6.1)
Accidental Overdose		
Reduced tolerance	738	47 (6.4)
Recent abstinence	823	41 (5)
Alcohol abuse	1220	109 (8.9)
Poly-substance	2615	155 (5.9)
Injecting		
Previously injecting	1433	102 (7.1)
Currently injecting	1047	81 (7.7)
High risk injector	515	49 (9.5)
Share injecting equipment	367	32 (8.7)
Violence		
Violent past	1051	45 (4.3)
Violent thoughts	84	5 (6)
Violent Behaviour	119	8 (6.7)
Violence Concern	117	10 (8.6)
Health BRSA Items		
BBV Infections	900	92 (10.2)
Hist of s.rel.sezures	588	59 (10)
Unmet needs	717	92 (12.8)
Cognitive impairment	220	24 (10.9)
High risk sexual behaviour	258	14 (5.4)
Social BRSA Items		
Homeless/unstable housing	1341	76 (5.7)
Childcare/social service problems	392	17 (4.3)
social isolation	1246	88 (7.1)
self-neglect	816	74 (9.1)
criminal activity	1037	47 (4.5)
Service Use Items		
Erratic engagement	880	56 (6.4)
Socio-demographic variables		
Age at assessment		
15–24	358	9 (2.1)
25–29	614	13 (2.1)
30–34	833	36 (4.3)
35–39	888	47 (5.3)
40–44	869	45 (5.2)
45–49	536	33 (6.2)
50+	390	44 (11.3)
Gender		
Males	3224	166 (5.2)
Females	1264	61 (4.8)
Ethnicity		
White British	3002	170 (5.7)
Other White	622	32 (5.1)
Black	466	15 (3.2)
Mixed, unknown & other	398	10 (2.5)
Level of deprivation (in tertiles)		
Low (2.19–27.42)	1468	67 (4.6)
Moderate (27.43–37.0)	1470	77 (5.2)
High (37.1+)	1474	82 (5.6)

vices. The completion of the BRSA-A assists in informing clinical staff whether a full risk screen is then required (SLaM, 2011).

The BRSA-A includes twenty-seven binary items (0 = no risk; 1 = risk detected). These individual items have been sub-classified into seven risk domains: suicidality, accidental overdose, injecting practices, violence, health, social, and service use. The full list of individual BRSA-A items and their classified risk domains are presented in Table 1. For analytical purposes we collapsed relevant BRSA-A items into three domains as exposures of interest—suicidality, likelihood of accidental overdose and unsafe injecting practice. The suicidality domain consisted of suicide attempt history, suicidal ideation, carer concern and major mental illness items. The likelihood of accidental overdose domain consisted of reduced tolerance, recent abstinence, alcohol abuse and poly-substance use. The unsafe injecting domain included previous/current injecting, high risk injecting, and sharing of injecting equipment items. A score of 1 was assigned if any item within a given risk domain was scored as present; or 0 if all items within that risk domain were scored as absent—this increased power for all-cause and cause-specific overdose investigations. We chose to focus on these three domains as exposures because of their likely impact relationship on mortality in this patient group (World Health Organisation, 2013). Remaining BRSA-A items were included in analyses individually, as potential confounders.

2.6. Statistical analysis

Having checked proportional hazards assumptions, Cox regression (Cox, 1972) survival analyses were used to model the associations between the suicidality, accidental overdose, unsafe injecting domains (obtained from the first BRSA-A assessment in the observation period) and all-cause mortality. Competing risk regression was performed to model cause-specific overdose deaths for the same domains. Patients' 'at risk' periods commenced from the date of their first BRSA-A assessment within the observation period (between 1 April, 2008 to 31 March, 2014) and ended on the day of their death or the end of observation period, whichever came first. We used likelihood ratio tests to examine potential interactions between risk domains and admissions to SLaM services in the two-month period after the assessment was conducted, and between risk domains and the OST prescriptions in the same observation period. Where a significant interaction was found we stratified the data accordingly and re-ran the Cox models with all-cause mortality as the outcome. Kaplan–Meier survival curves were used to visualize results for stratified analyses. All analyses were conducted using STATA 12, with significance levels at $p < 0.05$.

3. Results

The total number of patients with primary or secondary ICD10 F11 OUD diagnosis within the six-year period between 1st April, 2008 and 31st March, 2014 was 5335 and BRSA-A was completed for 84.1% (n = 4488) of those. There were no significant differences between age (calculated at midpoint observation period for this comparison), gender, ethnicity and mortality in people with and without completed BRSA-A assessments. There were no individual missing items within the group who had the BRSA-A completed. Therefore, the total number of individuals who met the inclusion criteria and whose data were extracted for analysis were 4488 (71.8% male; 66.9% "White British"), with 227 registered deaths (detailed in Table 1). Patients contributed a total of 17,804.59 at-risk person years. Age at risk assessment within our observation period ranged from 15 to 73 years with a mean age of 37.6 (SD = 9.07), and with mean age at death of 43.7 (SD = 9.15). More than a quarter (27.4%) of our OUD cohort were found to have a comorbid major mental illness. Majority of patients (64.2%) were admitted into SLaM services in the subsequent 2 months after their risk assessment was carried out.

Associations between suicidality, accidental overdose and unsafe injecting BRSA-A risk domains and all-cause mortality are represented in Table 2. In the fully adjusted models with all-cause mortality as an outcome, we found that BRSA-A assessed unsafe injecting and likelihood of accidental overdose was associated with increased risk of all-cause mortality (HR 1.53, 95% CI 1.10–2.11; HR 1.48, 95% CI 1.00–2.19 respectively).

We were able to obtain data on recorded underlying cause for 68.7% of deaths in our cohort (156/227), with overdose deaths

Table 2
Fully adjusted Cox and competing risk regression models examining associations between all-cause and cause-specific mortality and BRSA-A appraised suicidality, likelihood of accidental overdose and unsafe injecting in patients with opioid dependency.

Risk Cluster	Fully adj.[a] all-cause HR (95% CI)	p value[a]	Fully adj.[a] SHR for overdose[b] deaths (95% CI)	p value[a]	Fully adj.[a] SHR for deaths other than overdose (95% CI)	p value[a]
Suicidality						
None detected	Reference		Reference		Reference	
Detected (n = 1929, 120 deaths)	1.23 (0.92–1.64)	0.154	**2.89 (1.38–6.03)**	**0.005**	0.83 (0.55–1.26)	0.378
Likelihood of Accidental Overdose						
None detected	Reference		Reference		Reference	
Detected (n = 3416, 194 deaths)	**1.48 (1.00–2.19)**	**0.049**	2.82 (0.83–9.62)	0.097	1.23 (0.73–2.08)	0.43
Unsafe Injecting						
None detected	Reference		Reference		Reference	
Detected (n = 2249, 161 deaths)	**1.53 (1.10–2.11)**	**0.011**	**2.52 (1.11–5.70)**	**0.027**	1.37 (0.83–2.29)	0.221

Statistically significant ($p < 0.05$) hazard ratios are in bold
HR, hazard ratio; CI, confidence interval; SHR, sub-distribution hazard ratio.
[a] Adjusted for all variables listed in Table 1.
[b] Accidental and intentional overdoses.

Table 3
Cox regression analyses examining associations between suicide risk domain and all-cause mortality in individuals with opioid use disorder stratified by post BRSA-A admission to SLaM services.

	Hazard Ratio (95% CI), P value			
	Crude HR (95% CI)	p value	Fully adjusted[a] HR (95% CI)	p value[a]
Not admitted (N = 1602, 90 Deaths)				
No suicidality detected	Reference		Reference	
Suicidality detected (n = 631)	**2.37 (1.56–3.62)**	**<0.001**	**2.03 (1.67–3.24)**	**0.003**
Admitted (N = 2881, 137 Deaths)				
No suicidality detected	Reference		Reference	
Suicide risk detected (n = 1294)	1.27 (0.91–1.78)	0.162	0.91 (0.63–1.32)	0.636

HR, hazard ratio; CI, confidence interval.
Statistically significant ($p < 0.05$) hazard ratios are in bold.
[a] Adjusted for all variables listed in Table 1.

(both accidental and intentional) being the largest group (n = 44). Other predominant causes of deaths within this cohort were deaths from hepatic causes (n = 39) and infectious diseases (n = 35) (data not shown in tables). In the fully adjusted competing risk regression models we found that BRSA-A assessed suicidality and unsafe injecting risks were independently and significantly associated with increased overdose mortality (sub-distribution hazard ratio [SHR] 2.88, 95% CI 1.38–6.03; SHR 2.52, 95% CI 1.11–5.67 respectively). Likelihood of accidental overdose was not associated with fatal overdose in these analyses.

In view of the significant findings above, we tested for the presence of interactions between admission in the 2-month period immediately after BRSA-A assessment and (1) suicidality, (2) accidental overdose and (3) unsafe injecting domains, in models where the outcome was all-cause mortality. An interaction between BRSA-A suicide risk and SLaM admission was found. Additionally, in all-cause mortality models, we tested for interactions between the types of opioid substitute treatment (i.e., buprenorphine, methadone, Suboxone [buprenorphine/naloxone]) and the three BRSA-A risk domains mentioned above but none were found (data not in tables)

After stratifying the analysis by admission to SLaM services (presented in Table 3) we found that an association between BRSA-A suicidality and all-cause mortality was present in the group who had not been admitted into SLaM services in the two months after their risk assessment (HR 2.03, 95% CI 1.67–3.24), but not for the admitted group. The Kaplan–Meier survival curve in Fig. 1 visualizes results for suicide risk domain stratified by admission to SLaM service showing the reduced survival in BRSA-A patients where suicidality was assessed as being present who were not admitted. Of all those admitted, 65.9% were admitted to addiction services, with other most common admissions being to psychological medicine and psychosis departments (data not shown in tables).

To establish the cause of non-admission, a manual search (where all free-text clinical notes and correspondence were reviewed) in the electronic patient records was conducted in a random sample of 200 patients who were not admitted to services in the 2-month period after their risk assessment (n = 100 where suicidality was assessed as being present in their BRSA-A; n = 100 where suicidality was not evident). Of those where suicidality was classified as being present, a manual electronic patient data search revealed that the leading causes for non-admission were loss of contact with the patient (51%) and transfer out of services (26%). Similarly, in the sample where suicidality was not evident, the leading cause for non-admissions were loss of contact with the patient (48%), transfer out of services (22%) and incarceration (11%). No interactions between BRSA-A risks of unsafe injecting and likelihood of accidental overdose and admission to services were found.

4. Discussion

Three important findings arising from this study ought to be noted. First, addiction-specific brief risk screen assessment may provide useful information to identify subgroups at elevated risk of mortality. Second, specific domains within the BRSA-A were particularly informative. Suicidality was found to be associated with increased risk of overdose mortality; unsafe injecting practices were associated with both all-cause and overdose mortality; and increased likelihood of accidental overdose was associated with all-cause mortality but not fatal overdoses. Finally, suicidality was associated with a twofold increased all-cause mortality risk among OUD patients who were not admitted to mental health services within 2 months of their risk assessment. However, we found no

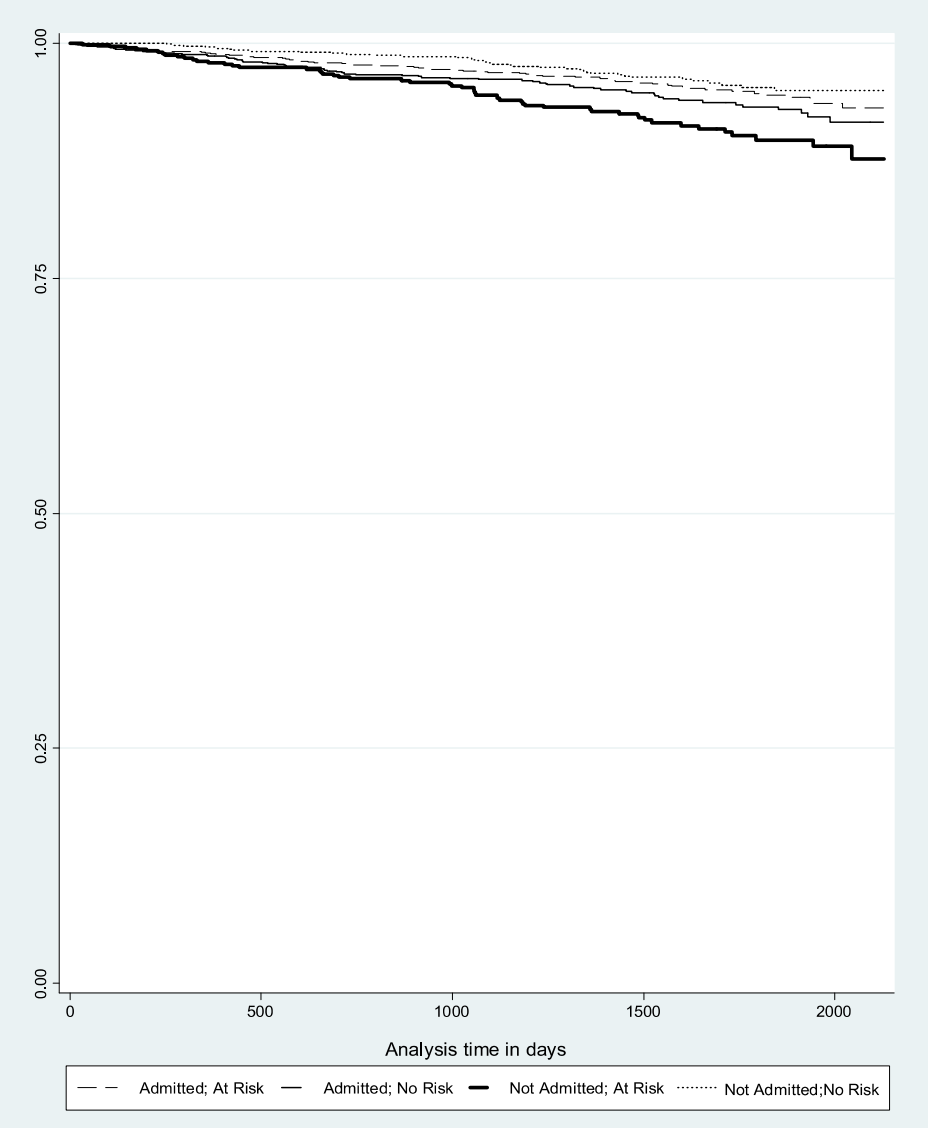

Fig. 1. Kaplan–Meier survival curve for BRSA-A suicidality domain and admissions to SLaM services (in days).

evidence that suicidality presented a similar risk in the subgroup who were admitted into mental health services during this time frame. These finding suggest that OUD patients with clinically evident suicidality who are not admitted to mental health services promptly may be particularly vulnerable

Whilst the relationship between drug injecting practices and increased all-cause and overdose mortality in OUD is consistent with current literature (Degenhardt et al., 2011; WHO, 2013), the relationship between overdose, suicide and intent is not as clear. Several studies have questioned to what extent heroin overdoses are de facto suicide attempts. An association between heroin overdose and suicide was noted, for example, in a study of 77 overdose survivors admitted to accident and emergency, with 49% reporting suicidal thoughts or feelings immediately prior to overdose (Neale, 2000). In another study among a London treatment sample, 50% of those with a history of overdose had two attempted suicides compared to 18% of those with no history of overdose (Vingoe et al., 2009). However, Darke and Ross, (2000) reported that while 40% of methadone maintenance participants had attempted suicide, only 10% had done so by means of a deliberate heroin overdose. Drug overdose was the most common method of attempted suicide, but by means of non-opioid pharmaceutical preparations. Conversely, heroin overdose among their participants overwhelmingly appeared to be accidental (92%).

Our data suggest that screening positively on at least one item within the suicidality domain, including suicide attempt and/or ideation, carer concern or major mental illness is, independently of accidental overdose risk factors, associated with an almost three-

fold increase in fatal overdose. Although we do not know whether fatal overdoses in our cohort were indeed caused by heroin, other drugs, or a mixture of the two, it is noteworthy that in 2014 in England and Wales, more than a half of all deaths from drug poisoning involved an opiate drug (ONS, 2015). Second, because intent was unknown, we do not know which overdose deaths in our cohort were accidental and which were suicides. However, we did find an association between suicidality and overdose fatalities and did not find associations between increased likelihood of accidental overdose and overdose fatalities. This could be interpreted either that most overdose fatalities were deliberate (suicides), or that identification of patients as 'likely to accidentally overdose' resulted in higher visibility to services which then resulted in improved healthcare. Increased likelihood of accidental overdose may be addressed within addiction services, for example, by overdose training or supply of naloxone antidote. However, suicidality may be much more complex and problematic to address and with the need for dual-diagnostic/multidisciplinary care plan approaches addressing high levels of underlying depression and other psychiatric comorbidities (Bogdanowicz et al., 2015; Cantor et al., 2001; Darke et al., 2007).

The elevated mortality risk in patients where suicidality was evident and who were not admitted to mental health services in the subsequent two months, highlights the importance of admission, access to services and treatment provision. McCowan et al. (2009) describe history of admission as being a risk factor for mortality in this patient group. However, our study suggests that timing of admission itself is a protective factor for those at risk. Furthermore, non-admission into services was largely due to loss of contact and transfers out of service/catchment area. Drop-out from treatment (and relapse) and erratic engagement in services appears to be highly prominent in this patient group, and both are known to increase mortality considerably (Degenhardt et al., 2011; Zanis and Woody, 1998). Similarly, times of transition between services involved in the care of people with opioid dependency are particularly 'risky', for example after release from prison (Merrall et al., 2010). OUD patients who are assessed as being at risk of suicide and subsequently disengage with current services may require more determined strategies for patient follow-ups and service transition due to their high risk of mortality. Without better outreach for these poorly engaging groups, current policy will broaden inequalities for more vulnerable groups.

The results of this study need to be considered in light of certain limitations, alongside acknowledgement of strengths. SLaM is a large provider of secondary mental healthcare in Europe, with close to 100% monopoly provision to its geographic catchment. As a result, we were able to draw on electronic addictions service clinical records of almost five thousand OUD patients providing the statistical power to simultaneously control for a range of potential confounders. The inclusion criteria specified primary or secondary OUD diagnosis. Whilst the use of NLP applications allowed us to supplement the existing structured fields, it did not allow to us establish whether these diagnosis were primary or secondary and measure its impact on outcomes.

SLaM patient death-tracing is regularly updated and is based on death certificates issued across the UK for both active and non-active SLaM patients. This is not the case for underlying cause of death, which derives from additional static ONS linked data. Information on underlying cause of death was only present in 69% of cases. Additionally, as discussed, we could not differentiate between intentional (i.e., suicide-related) and non-intentional (i.e., accidental) overdose deaths. Similarly, toxicology reports were not available, and it was therefore unclear which drugs were involved in overdose deaths.

The clinical risk assessment information used for analysis was the first within the observation period but may not have been the first risk assessment conducted in an individual's lifetime. Given the mean age of our cohort as 37, there will be individuals who have had previous treatment episodes, and subsequently previous risk assessment conducted, occurring prior to our observation period. Similarly, we do not know if any and which circumstantial/treatment changes occurred in the period beyond the subsequent two months after their risk screen and until their death/end of observation period, which might have influenced mortality risk in addition to clinically appraised suicide risk. However, given that a high proportion of people did not enter treatment due to loss of contact, it seems that the combination of suicidality and erratic engagement in services increases mortality in the longer term.

It is important to note that our analysis investigated admissions to mental health services across SLaM, and not addictions only. We chose to broaden our focus because suicide risk in OUD may not necessarily be attended to within the addiction setting in the first instance, especially in cases of psychiatric comorbidity. The identification of reasons for non-admission was extracted from a random sample and not the entire non-admitted sub-cohort. Although the administration of BRSA-A assessments is mandated in practice, only 84% of OUD patients had the BRSA-A scale completed. Finally, more consideration has to be given to the brief risk assessment screen as a measure of exposure status, which has advantages and disadvantages. The BRSA-A was not formally evaluated as a measurement in terms of constructs such as inter-rater or test-retest reliability, or its discriminant validity. However, this is a real-world measure, developed by clinicians and is actively used in daily practice, representing valuable and current real-life scenarios.

Prompt identification of those at risk is key. Our study provides evidence that addiction-specific risk assessment may be useful in predicting mortality in a timely manner. The study also points out associations between suicidality and overdose mortality in people with opioid dependency, and highlights the importance of admission to mental health services for those where suicidality is evident. Prompt identification and management of those at risk using brief risk assessment may be useful to save time, save costs and, most importantly, to save lives.

Conflict of interest

RH and RS have received research funding from Roche, Pfizer, J&J and Lundbeck. JS has conducted a variety of research studies of addictive disorders and treatments and through the university, has provided consultancy to pharmaceutical companies about new treatments for opioid addiction, including Martindale, MundiPharma and Braeburn (none was the subject of study in this work). For further description see:
www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. Other authors have no conflict of interest.

Contributions

All the authors listed contributed to the process of hypothesis generation, data collection, statistical analyses, or manuscript preparation, and fulfilled the criteria for authorship. Additionally, KMB wrote the manuscript and analyzed data. RDH and JS were primary supervisors. RS was responsible for securing funding for CRIS and constituent studies. MZ, JD, CKC (and all other authors) provided their suggestions during analysis and manuscript review process. HS is responsible for data extraction for analysis.

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References

Bogdanowicz, K.M., Stewart, R., Broadbent, M., Hatch, S.L., Hotopf, M., Strang, J., Hayes, R.D., 2015. Double trouble: psychiatric comorbidity and opioid addiction-all-cause and cause-specific mortality. Drug Alcohol Depend. 148, 85–92, http://dx.doi.org/10.1016/j.drugalcdep.2014.12.025.

Cantor, C., McTaggart, P., De Leo, D., 2001. Misclassification of suicide-the contribution of opiates. Psychopathology 34, 140–146, 49297.

Chang, C.K., Hayes, R.D., Broadbent, M., Fernandes, A.C., Lee, W., Hotopf, M., Stewart, R., 2010. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry 10, 77, http://dx.doi.org/10.1186/1471-244x-10-77.

Cox, D.R., 1972. Regression models and life-tables. J. R. Stat. Soc. 34, 187–220.

Darke, S., Ross, J., 2000. The Relationship Between Suicide And Overdose Among Methadone Maintenance Patients. NDARC Technical Report, No. 100, Sydney, Australia.

Darke, S., Ross, J., 2002. Suicide among heroin users: rates, risk factors and methods. Addiction 97, 1383–1394.

Darke, S., Dagenhardt, L., Mattick, R., 2007. Mortality Amongst Illicit Drug Users: Epidemiology, Causes And Intervention. Cambridge University Press, Cambridge, UK.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., McLaren, J., 2011. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 106, 32–51, http://dx.doi.org/10.1111/j.1360-0443.2010.03140.x.

Department of Health (England) and the devolved administrations (2007). Drug Misuse and Dependence: UK Guidelines on Clinical Management. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive.

Harriss, L., Hawton, K., 2005. Suicidal intent in deliberate self-harm and the risk of suicide: the predictive power of the Suicide Intent Scale. J. Affect. Disord. 86, 225–233, http://dx.doi.org/10.1016/j.jad.2005.02.009.

Hayes, R.D., Chang, C.K., Fernandes, A., Broadbent, M., Lee, W., Hotopf, M., Stewart, R., 2011. Associations between substance use disorder sub-groups, life expectancy and all-cause mortality in a large British specialist mental healthcare service. Drug Alcohol Depend. 118, 56–61, http://dx.doi.org/10.1016/j.drugalcdep.2011.02.021.

Hayes, R.D., Chang, C.K., Fernandes, A., Begum, A., To, D., Broadbent, M., Hotopf, M., Stewart, R., 2012. Associations between symptoms and all-cause mortality in individuals with serious mental illness. J. Psychosom. Res. 72, 114–119, http://dx.doi.org/10.1016/j.jpsychores.2011.09.012.

Kapur, N., 2005. Management of self-harm in adults: which way now? Br. J. Psychiatry 187, 497–499, http://dx.doi.org/10.1192/bjp.187.6.497.

McCowan, C., Kidd, B., Fahey, T., 2009. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. BMJ 338, b2225, http://dx.doi.org/10.1136/bmj.b2225.

Merrall, E.L., Kariminia, A., Binswanger, I.A., Hobbs, M.S., Farrell, M., Marsden, J., Hutchinson, S.J., Bird, S.M., 2010. Meta-analysis of drug-related deaths soon after release from prison. Addiction 105, 1545–1554, http://dx.doi.org/10.1111/j.1360-0443.2010.02990.x.

National Treatment Agency for Substance Misuse [NTA], 2006a. Models of Care for Treatment of Adult Drug Misusers: Update 2006. National Treatment Agency for Substance Misuse, London, UK.

National Treatment Agency for Substance Misuse [NTA], 2006b. Care Planning Practice Guide. National Treatment Agency for Substance Misuse, London, UK.

Neale, J., 2000. Suicidal intent in non-fatal illicit drug overdose. Addiction 95, 85–93.

Office For National Statistics (ONS), 2011. Impact of Registration Delays on Mortality Statistics. Office For National Statistics, London UK.

Office For National Statistics (ONS), 2015. Deaths related to drug poisoning in England and Wales, 2014 registrations, Statistical Bulletin.

Perera, G., Broadbent, M., Callard, F., Chang, C.-K., Downs, J., Dutta, R., Fernandes, A., Hayes, R., Henderson, M., Jackson, R., Jewell, A., Kadra, G., Little, R., Prichard, M., Shetty, H., Tulloch, A., Stewart, R., 2016. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record derived data resource. BMJ Open 6 (3), http://dx.doi.org/10.1136/bmjopen-2015-008721, e008721.

South London and Maudsley NHS Foundation Trust, 2011. Policy For Clinical Risk Assessment And Management of Harm. South London and Maudsley NHS Foundation Trust, London, UK.

Stewart, R., Soremekun, M., Perera, G., Broadbent, M., Callard, F., Denis, M., Hotopf, M., Thornicroft, G., Lovestone, S., 2009. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 9, 51, http://dx.doi.org/10.1186/1471-244x-9-51.

Sultana, J., Chang, C.K., Hayes, R.D., Broadbent, M., Stewart, R., Corbett, A., Ballard, C., 2014. Associations between risk of mortality and atypical antipsychotic use in vascular dementia: a clinical cohort study. Int. J. Geriatr. Psychiatry 29, 1249–1254, http://dx.doi.org/10.1002/gps.4101.

Vingoe, L., Welch, S., Farrell, M., Strang, J., Vingoe, L., Welch, S., Farrell, M., Strang, J., 2009. Heroin overdose among a treatment sample of injecting drug misusers: accident or suicidal behaviour? J. Subst. Use 4, 88–91.

Wand, T., 2012. Investigating the evidence for the effectiveness of risk assessment in mental health care. Issues Mental Health Nurs. 33, 2–7, http://dx.doi.org/10.3109/01612840.2011.616984.

World Health Organisation (WHO), 2013. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull. World Health Organ. 91, 102–123, http://dx.doi.org/10.2471/BLT.12.108282.

World Health Organisation (WHO), 2014. Community Management of Opioid Overdose. World Health Organisation, Geneva, Switzerland, 10.1007.

World Health Organization, 1993. The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic Criteria For Research, Geneva.

Wu, C.-Y., Chang, C.-K., Hayes, R.D., Broadbent, M., Hotopf, M., Stewart, R., 2012. Clinical risk assessment rating and all-cause mortality in secondary mental healthcare: the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register. Psychol. Med. 42, 1581–1590, http://dx.doi.org/10.1017/S0033291711002698.

Zanis, D.A., Woody, G.E., 1998. One-year mortality rates following methadone treatment discharge. Drug Alcohol Depend. 52, 257–260.

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Double trouble: Psychiatric comorbidity and opioid addiction—All-cause and cause-specific mortality

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ABSTRACT

Background: Opioid misusers have recognized high mortality but the influence of psychiatric comorbidity in excess cause-specific mortality is unclear.
Methods: Opioid use disorder (OUD) patients were identified in the South London and Maudsley Case Register. Deaths were identified through database linkage to the national mortality dataset. Standard mortality ratios were calculated to compare mortality risk with the general population. Cox and competing risk regression models were used to investigate the effect of psychiatric comorbidity and psychological health on all-cause and cause-specific mortality (respectively) in OUD patients.
Results: Of 4837 OUD patients, 176 had died. Mortality rates were substantially higher than the general population (SMR 4.23; 95%CI 3.63–4.90). Among those with OUD, comorbid personality disorder (PD) and comorbid alcohol use disorder (AUD) was associated with increased all-cause mortality in all models, including the fully adjusted model, controlling for socio-demographic factors, severity of drug use, risk behaviours and physical health (HR2.15, 95%CI 1.17–3.95; HR2.28, 95%CI 1.54–3.36). AUD was associated with increased risk of fatal overdose (HR2.57, 95%CI 1.26–5.26) and hepatic-related deaths (HR7.26, 95%CI 2.79–18.86). Individuals with OUD and comorbid PD had almost four times greater risk of liver related deaths compared to those without PD (HR3.76, 95%CI 1.21–11.74). Comorbid severe mental illness and poor psychological health were not associated with increased mortality.
Conclusions: This study highlights the importance of assessment for PD and AUD in OUD patients in order to identify individuals at substantially elevated mortality risk to enable a more personalized approach to their medical care.

1. Introduction

Opioid dependent individuals are at substantially higher risk of mortality compared to the general population, to those with other drug-use disorders (Harris and Barraclough, 1998; Hayes et al., 2011) and to people with severe mental illnesses (SMI; i.e., psychotic disorders and bipolar affective disorder, Chang et al., 2010; Dickey et al., 2004; Harris and Barraclough, 1998). Previous research has found that individuals with substance use disorders, especially opioid dependence, have more than four times the expected risk of mortality, with life expectancies reduced by more than nine years compared to national norms. This difference was most pronounced in females whose life expectancy was reduced by more than 17 years (Hayes et al., 2011).

Although there is evidence of the link between opioids and elevated mortality risk, factors which may predispose some opiate users to higher or lower mortality risk compared to their peers with the same disorder are not properly understood. Existing literature on such risk factors is mixed, with substantial international (Bargagli et al., 2006; Darke and Ross, 2002), and chorological differences (Ghodse et al., 1985; Shah et al., 2008).

Substance use disorders are strongly associated with other psychiatric disorders in both clinical (Brooner et al., 1997; Weaver et al., 2003) and population samples (Rodriguez-Llera et al., 2006). Lifetime comorbidity with other psychiatric disorders range from 44% to 93% (Brooner et al., 1997; Cacciola et al., 2001; Khantzian and Treece, 1985; King et al., 2000; Krausz et al., 1999; Mason et al., 1998). Psychiatric comorbidity is associated with poor treatment prognosis, greater psychosocial impairment, increased risk of

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relapse and higher rates of HIV risk behaviour (Arendt et al., 2007; Brooner et al., 1997; Darke and Ross, 1997; Disney et al., 2006; Landheim et al., 2006; Rounsaville et al., 1982, 1986). Comorbid alcohol problems are highly prevalent in this patient population (25%) (Gossop et al., 2001) and are reportedly associated with an increased risk of fatal overdose (Darke and Ross, 1997). Mood and anxiety problems (41%), personality disorders (PD) (40%) and psychotic disorders (12%) are found to be the common comorbid diagnosis not only in opioid users (Rodriguez-Llera et al., 2006) but also in other drug users (Weaver et al., 2003). Antisocial personality disorder is a rare diagnosis in the general community (4%) (Robins and Regier, 1991), but occurs at rates of up to 65% in heroin-using samples (Bargagli et al., 2006; Darke et al., 1994). In addition, people with a diagnosis of PD have a four-fold higher mortality, with substantially reduced life expectancy (Fok et al., 2012). Similarly, substantially higher mortality rates are found in people with SMI and depressive disorders when compared to the general population (Chang et al., 2010). In spite of this, the impact of psychiatric comorbidity on mortality risk in substance use disorders has received only moderate attention, with existing investigations reporting mixed results (Arendt et al., 2011; Davoli et al., 1993; Gossop et al., 2002; Mattisson et al., 2011).

Given the high prevalence of comorbid alcohol, mood problems, PD and SMI among opioid users, and particularly high hazard ratios for mortality risk in individuals with these diagnoses, it is plausible that these psychiatric problems may contribute to the elevated mortality risk observed in this patient group, with regard to both natural and unnatural causes of death. Investigating the impact of comorbid psychiatric problems in opioid users and looking beyond unnatural causes of mortality may help improve our understanding of the pathways to premature mortality among opioid users as well as identifying subgroups at substantially elevated mortality risk. We used a large and well-established South London and Maudsley (SLaM) case register (Stewart et al., 2009) to explore these relationships more fully. The study described here investigates the associations between subjective ratings of psychological health, such as feelings of depression and anxiety, comorbid diagnosis of PD, SMI and AUD, in relation to all-cause as well as cause-specific mortality in a large cohort of opioid-dependent patients receiving secondary mental healthcare.

2. Method

2.1. Study setting

SLaM is one of the largest specialist mental healthcare services in Europe, which provides, within the framework of the British National Health Service (NHS), comprehensive mental healthcare and addiction services to a catchment population of approximately 1.2 million residents across seven multicultural, ethnically diverse, highly dense boroughs of London. Within the framework of NHS in the United Kingdom, mental health trusts have close to 100% monopoly for service provision to its geographic catchment. Electronic health records (EHRs) have been used comprehensively across most SLaM services since 2006 and across addiction services since April 2008. In 2008 the CRIS system, linked with mortality tracing at a national level, was developed at the SLaM NIHR Biomedical Research Centre for Mental Health, which enables researchers to search and retrieve EHRs in a de-identified form, with more than 250,000 cases currently represented on the system. The protocol for the SLaM case register has been described in detail elsewhere (Stewart et al., 2009). CRIS is approved as a dataset for secondary analysis by Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5).

2.2. Inclusion criteria

Diagnoses in CRIS are coded according to the 10th edition of the World Health Organization International Classification of Diseases (ICD-10; WHO, 1993). In this analysis, the sample comprised a cohort of 4837 SLaM patients who were diagnosed with an ICD-F11 opioid use disorder within the period between 1st April, 2008 and 31st December, 2012 (inclusive) and who had been assessed by a clinician using the National Drug Treatment Monitoring System (NDTMS) and the Treatment Outcome Profile (TOP; Marsden et al., 2008) at least once during the observation period. All drug treatment agencies must provide a basic level of information to the National Drug Treatment Monitoring System (NDTMS) on their activities each month. The TOP is a reliable and valid 20-item instrument for monitoring substance misuse treatment outcomes and is designed to capture pertinent features such as substance use, health risk behaviour, offending, health and social functioning; and both NDTMS and TOP are now firmly embedded in the routine in-treatment monitoring of outcomes across the UK. In the SLaM case register, OUD is the second most frequently diagnosed substance use disorder after AUD (Hayes et al., 2011) and approximately 96% of SLaM patients with an OUD, within the observation period, appeared on the NDTMS and 89% had the TOP completed on at least one occasion.

2.3. Main outcome measures

The main outcome in this study was mortality, within the period 1st April, 2008 to 31st December, 2012 (inclusive), in individuals with primary or secondary OUD. Routine mortality identification is performed on a monthly basis by SLaM through a linkage to the national mortality base using the unique NHS number assigned to all UK citizens. Every death in the UK must be reported to the Office for National Statistics General Records Office, which is then conveyed to the NHS Care Records Service and available to all NHS organizations. This mortality tracing allowed us to establish who had died during the observation period and includes active as well as non-active SLaM cases. The full procedure for identifying and confirming SLaM patient deaths has been described elsewhere (Chang et al., 2010). In addition, a linkage to data specifically derived from death certificates allowed us to establish the recorded underlying cause of each death. Based on death data extracted within our cohort, ICD-10 codes A00-B99 were classified as infectious diseases; codes C220, K703-K769 were classified as alcoholic and other hepatic diseases; codes C349, J13-J449 were grouped as pneumonia and other pulmonary diseases; codes V01-Y98 were classified as unnatural causes, with codes X420-X450, Y120, Y125 sub-classified as overdose deaths. The remainder of ICD-10 cause of death codes within this cohort related to other natural causes of mortality and were classified as such. These groupings were based on the most common causes of mortality in this patient group where groups had sufficient power to allow for multivariate analysis.

2.4. Explanatory variables

The main characteristics of interest in this study were psychological health and psychiatric comorbidity, measured by investigation of four aspects of mental health, including patients' subjective psychological health ratings, and comorbid diagnosis of a SMI, PD and AUD.

Psychological health status data, a subjective 21-point scale rating, was extracted from the TOP. Cohort members were classified as having a comorbid diagnosis of SMI if they had received at least one of the following diagnoses during the observation period: schizophrenia (ICD-F20), schizoaffective disorders (ICD-F25), and bipolar affective disorder (ICD-F31). Similarly, the cohort was classified as having a comorbid diagnosis of PD if they had received either a specific personality disorder (ICD-F60) or mixed and other personality disorder diagnosis (ICD-F61), and a comorbid diagnosis of AUD if they had received an ICD-F11 alcohol use disorder diagnosis. Consequently those with more than one comorbid diagnosis could appear in more than one category.

In addition to the main exposures of interest, an extensive list of other covariates derived from TOP and NDTMS were considered as potential confounders. Date of birth, ethnicity and gender are routinely recorded on SLaM electronic patient records in their designated fields. Age was calculated from the date on which individuals received their ICD-F11 OUD diagnosis within the observation period. Ethnic classifications were condensed into "White British", "Other White background", "African, Caribbean and other black background", and "Mixed, unknown and other". The level of deprivation for the neighbourhoods was established by linking the patient's residential postcode to the UK Census data projected for 2007. The full procedure for measuring level of deprivation is described elsewhere (Hayes et al., 2012). Severity of drug use included 'age at first primary problem drug, frequency of opioid use in the past 28 days' and a 'total number of different drugs used', reported within the observation window. Other variables included risk behaviours (injecting) and physical health rating. Likelihood ratio tests indicated that it was acceptable to include psychological and physical health rating, age at first diagnosis, level of deprivation and the total number of different drugs used as continuous variables.

2.5. Statistical analysis

Standardized mortality ratios (SMRs) using indirect standardization in STATA 12 for the period between 1 April, 2008 and 31 December, 2012 were calculated. The numerator was the number of deaths observed in SLAM records within the observation period and the denominator was the number of deaths we would expect to occur over the observation period based on age and gender specific death rates for the England and Wales population in 2008 (ONS, 2009). SMRs were age-standardized using 5-year age bands and stratified by gender, and are presented in Table 2. Cox regression (Cox, 1972) for survival analysis was used to model the associations of psychological health and psychiatric comorbidity with all-cause mortality. Competing risk regression was performed to model cause-specific mortality in our sample.

Patient's 'at risk' period commenced from the date of their first OUD diagnosis within the observation period between 1 April, 2008 and 31 December, 2012 and

ended on the day of their death or the end of observation period for individuals who survived. Associations between psychological status/comorbidity (psychological health rating, comorbid SMI, comorbid PD, comorbid AUD) and all-cause mortality were estimated after adjusting for the following blocks of variables: (i) age at diagnosis and gender, (ii) socio-demographic factors (age at diagnosis, gender, ethnicity, deprivation level, relationship status), (iii) age at diagnosis, gender and severity of drug use (age at first use, frequency of opiate use in past 4 weeks, total number of drugs used); (iv) age at diagnosis, gender and risk behaviours (intravenous drug administration); (v) age at diagnosis, gender and physical health; (vii) adjusted for all of the above, including the principal exposures of interest (fully adjusted model). Furthermore, associations with overdose deaths, hepatic disease deaths (two largest sub-cohorts), and all other causes of deaths; and psychological well-being were re-calculated using the competing risk regression models. Interactions between mortality and age and gender were also tested. All variables used in this analysis are listed in Table 1.

3. Results

The characteristics of the sample are reported in Table 1. The total number of individuals extracted from CRIS who met the inclusion criteria was 4837 (71% male; 68% "White British"), with 176 deaths registered within this cohort. Patients contributed a total of 14,782.136 person years at risk. Age at diagnosis within observation our observation window ranged from 14 to 86 years with a mean age of 37.5 years—although, this may not have been patients' first approach to addiction services over their lifetime. Individuals diagnosed aged 70 and over ($n = 15$) were primarily diagnosed for medical reasons and/or were in OUD treatment prior to April 2008 (i.e. prior to start of analytical observation window).

Mortality rates in this cohort were substantially higher than the general population (Table 2) (SMR 4.23; 95% 3.63–4.90), especially for women with OUD where rate was over five times the general population (SMR 5.69; 95%CI 4.16–7.59). To explore this elevated risk in more detail we proceeded to identify specific factors associated with mortality in this cohort.

Table 3 summarizes findings from initial Cox regression models of factors potentially associated with all-cause mortality in patients with OUD. Associations between psychological health and all-cause mortality remained the same after adjustment for age and gender. Better psychological health status was protective (HR 0.96, 95%CI 0.92–0.99, $p = 0.013$, per unit increase in the psychological health status scale), while those with co-morbid personality and alcohol use disorders were at increased risk of mortality after age and gender adjustment (HR 2.04, 95%CI 1.23–3.36, $p = 0.006$; HR 2.42, 95%CI 1.77–3.28, $p < 0.001$). No associations were found between severe mental illness and mortality. Age at diagnosis, increased level of deprivation, and intravenous drug administration were also all associated with an increased risk of mortality in the adjusted models. Initiation of drug use between ages 20 and 24 was associated with decreased mortality risk when compared to younger age at first use. Similarly, being in a relationship, good/moderate physical health and ethnicity other than white were associated with decreased mortality.

Table 4 displays Cox regression associations between psychiatric co-morbidities and all-cause mortality after controlling for blocks of variables. Better psychological health status on a 20-point scale was associated with lower risk of mortality when adjusted for socio-demographic factors (HR 0.95 per unit increment, 95%CI 0.91–0.99, $p = 0.007$), but not after adjustment for other factors. Comorbid diagnosis of SMI was not significantly associated with mortality in this cohort. However the presence of comorbid PD or AUD were found to be associated with increased mortality in all models, including the fully adjusted model (HR 2.15, 95%CI 1.17–3.95, $p = 0.014$; HR 2.28, 95%CI 1.54–3.36, $p = 0.000$, respectively). In addition, we tested for the presence of interactions between mortality and age and gender, however, none were detected (data not shown).

We were able to obtain data on recorded underlying cause for 83% of deaths in our cohort (146/176) and these are presented in

Table 1
Cohort characteristics.

Variables	Number of individuals (%)	Number of deaths (%)
Total	4837	176 (4)
Psychiatric well-being		
Psychological health rating (0–20, in tertiles)		
Poor (0–8)	1318 (27)	57 (32)
Moderate (9–12)	1477 (31)	49 (28)
Good (13–20)	1452 (30)	39 (22)
Missing	590 (12)	31 (18)
Comorbid SMI disorder		
No	4500 (93)	162 (92)
Yes	337 (7)	14 (8)
Comorbid personality disorder		
No	4564 (94)	159 (90)
Yes	273 (6)	17 (10)
Comorbid alcohol use disorder		
No	3860 (80)	109 (62)
Yes	977 (20)	67 (38)
Socio-demographic variables		
Age group at first F11 diagnosis		
14–24	415 (9)	8 (5)
25–29	693 (14)	12 (7)
30–34	872 (18)	26 (15)
35–39	949 (20)	37 (21)
40–44	938 (19)	31 (18)
45+	970 (20)	62 (35)
Missing	0	0
Gender		
Female	1404 (29)	46 (26)
Male	3433 (71)	130 (74)
Ethnicity		
White British	3266 (68)	140 (74)
Other White	595 (12)	22 (13)
Black	516 (11)	10 (6)
Mixed, unknown & other	460 (10)	4 (2)
Level of deprivation (0–100, in tertiles)		
Low (2.6–28.5)	1362 (28)	41 (230
Moderate (28.6–38.2)	1376 (28)	54 (31)
High (38.3+)	1393 (29)	56 (32)
Missing	706 (15)	25 (14)
Relationship status		
Not in a relationship	4215 (87)	163 (93)
In a relationship	390 (8)	9 (5)
Missing	232 (5)	4 (2)
Severity of drug use		
Age group at first use		
0–14	378 (8)	17 (10)
15–19	1391 (29)	69 (39)
20–24	948 (20)	20 (11)
25–29	578 (12)	14 (8)
30+	754 (16)	28 (16)
Missing	788 (16)	28 (16)
Days of opiate use in past 4 weeks		
None	1534 (32)	62 (35)
1–27	1337 (28)	36 (20)
Everyday	1398 (29)	48 (27)
Missing	568 (12)	30 (17)
Total number of different drugs used		
1	848 (18)	34 (19)
2	1398 (29)	50 (28)
3	1349 (28)	52 (29)
4+	1242 (26)	40 (23)
Risk behaviours		
Injected		
Not injected	3227 (67)	92 (52)
Injected	1382 (29)	72 (41)
Missing	228 (5)	12 (7)
Physical health		
Physical health status (0–20, in tertiles)		
Poor (0–9)	1283 (27)	79 (45)
Moderate (10–13)	1451 (30)	42 (24)
Good (14–20)	1514 (31)	24 (14)
Missing	589 (12)	31 (18)

Table 2
Indirect age-standardized mortality ratios stratified by gender for opioid use disorder diagnosis in SLAM compared to population of England and Wales in 2008.

	n	Expected deaths	Observed deaths	SMR (95%CI)
Total	4837	41.6	176	4.23 (3.63–4.90)
Female	1404	8.1	46	5.69 (4.16–7.59)
Male	3433	33.6	130	3.87 (3.24–4.60)

Table 5. Overdose was the most common cause of death (31%). When causes of death were grouped into natural/unnatural causes, the majority of deaths were due to natural causes (61%) with liver disease being the largest natural cause subgroup (23%). The mean age at death was 43 years but the difference between mean age at death between those dying from unnatural and natural causes was almost a decade. AUD and PD were independently associated with increased risk of mortality by liver disease (Table 6.) (SHR 7.28, 95%CI 2.65–19.97, $p < 0.001$; SHR 3.82, 95%CI 1.40–10.46, $p = 0.01$). AUD was also significantly associated with overdose deaths (SHR 2.53, 95%CI 1.14–5.61, $p = 0.02$). No significant associations were found for deaths by causes other than the above. Of those who died of alcoholic and other hepatic causes, 65% had previously received an AUD diagnosis on the EHR system (data not shown).

4. Discussion

Our analyses have shown that individuals with OUD have more than four times the risk of mortality compared to the general population. We then identified a further two-fold increased risk of all-cause mortality in OUD patients with personality and alcohol use disorders, compared to those without these comorbidities. Those with AUD in addition to OUD had twice the risk of fatal overdose and a more than seven-fold higher risk of death caused by hepatic related diseases. Those with comorbid personality problems were at almost four-fold risk of death of hepatic disease, compared to OUD patients without PD. However, no associations between mortality and serious mental illness, and psychological status were found.

Table 3
Crude and age and gender adjusted Cox regression models for associations with all-cause mortality in individuals with opiate use disorder (OUD).

	Crude hazard ratio (95%CI)	Adjusted by age & gender	Age & gender adjusted *p* value
Psychiatric well-being			
Psychological health status[*]	**0.96 (0.92–0.99)**	**0.96 (0.92–0.99)**	**0.013**
Comorbid serious mental illness			
Not Present	Referent	Referent	
Present	1.21 (0.70–2.09)	1.18 (0.69–2.05)	0.544
Comorbid personality disorder			
Not Present	Referent	Referent	
Present	**1.90 (1.15–3.13)**	**2.04 (1.23–3.36)**	**0.006**
Comorbid alcohol use disorder			
Not Present	Referent	Referent	
Present	**2.48 (1.83–3.37)**	**2.42 (1.77–3.28)**	**<0.001**
Socio-demographic factors			
Age at first F11 diagnosis[**]	**1.04 (1.03–1.06)**	**1.04 (1.03–1.06)**	**<0.001**
Gender			
Female	Referent	Referent	
Male	1.16 (0.83–1.62)	1.08 (0.77–1.52)	0.643
Ethnicity			
White British	Referent	Referent	
Other White	0.94 (0.60–1.47)	0.95 (0.61–1.49)	0.820
Black	**0.46 (0.24–0.87)**	**0.45 (0.24–0.86**	**0.016**
Other and unknown	**0.21 (0.08–0.56)**	**0.24 (0.89–0.65)**	**0.005**
Level of deprivation[**]	1.01 (1.00–1.03)	1.01 (1.00–1.24)	0.178
Relationship status			
Not in a relationship	Referent	Referent	
In a relationship	0.60 (0.31–1.18)	**0.50 (0.25–0.99)**	**0.045**
Severity of drug use			
Age at first use			
0–14	Referent	Referent	
15–19	1.07 (0.63–1.81)	1.09 (0.64–1.85)	0.754
20–24	**0.46 (0.24–0.88)**	**0.47 (0.25–0.90)**	**0.021**
25–29	0.52 (0.26–1.06)	0.50 (0.25–1.02)	0.106
30+	0.83 (0.46–1.52)	0.60 (0.33–1.12)	0.106
Frequency of opiate use			
None	Referent	Referent	
1 day–27 days	**0.62 (0.41–0.93)**	0.67 (0.44–1.01)	0.056
Everyday	0.77 (0.53–1.12)	0.89 (0.61–1.31)	0.558
Total number of drugs used[**]	0.98 (0.88–1.08)	0.99 (0.90–1.10)	0.862
Risk behaviours			
Injected			
Not injected	Referent	Referent	
Injected	**1.77 (1.30–2.41)**	**1.78 (1.31–2.43)**	**<0.001**
Physical health			
Physical health status[*]	**0.90 (0.87–0.93)**	**0.90 (0.87–0.93)**	**<0.001**

Statistically significant ($p < 0.05$) hazard ratios are in bold.

[*] Continuous variable, calculated per unit increase in the psychological/physical health status scale. The higher the score for psychological/physical scale, the better the psychological/physical health status.

[**] Continuous variable, calculated per unit increase in the deprivation score. The higher the score, the higher the level of deprivation/older age at first F11 diagnosis/higher number of total drugs used.

Table 4
Cox regression analyses of associations between psychological health and all-cause mortality in individuals with opiate use disorder (OUD).

	HR Adj. for sociodemographic factors[a] (95%CI)	HR Adj. for age, gender & severity of drug use[b] (95%CI)	HR Adj. for age, gender & risk behaviours[c] (95%CI)	HR Adj. for age, gender & physical health[d] (95%CI)	Fully adjusted model[e] (95%CI)
Psychological well-being					
Psychological health status	**0.95 (0.91–0.99)**	0.97 (0.93–1.00)	0.97 (0.93–1.01)	1.02 (0.98–1.06)	1.01 (0.97–1.06)
Comorbid serious mental illness					
Not present	Referent	Referent	Referent	Referent	Referent
Present	1.23 (0.70–2.18)	0.99 (0.50–1.96)	1.14 (0.63–2.05)	0.90 (0.46–1.77)	0.72 (0.34–1.53)
Comorbid personality disorder					
Not present	Referent	Referent	Referent	Referent	Referent
Present	**2.04 (1.19–3.49)**	**2.01 (1.15–3.52)**	**2.10 (1.25–3.53)**	**2.33 (1.38–3.93)**	**2.15 (1.17–3.95)**
Comorbid alcohol use disorder					
Not present	Referent	Referent	Referent	Referent	Referent
Present	**2.38 (1.71–3.31)**	**2.47 (1.73–3.53)**	**2.42 (1.77–3.32)**	**2.24 (0.88–3.13)**	**2.28 (1.54–3.36)**

[a] Age at OUD diagnosis, gender, ethnicity, level of deprivation, relationship status.
[b] Age at OUD diagnosis, gender, frequency of opiate use, age at first use, total number of different drugs used.
[c] Age at OUD diagnosis, gender, intravenous drug administration.
[d] Age at OUD diagnosis, gender, physical health rating.
[e] Adjusted for all variables in Table 3.
Statistically significant ($p < 0.05$) hazard ratios are in bold.

Table 5
Underlying causes of death among opioid dependent individuals.

Underlying cause of death	*N* (%)	Males (%)	Females (%)	Mean age at death (SD)
Overdose	45 (31)	26 (18)	19 (13)	38 (7.93)
Alcoholic and unspecified liver disease	34 (23)	27 (18)	7 (5)	45 (8.52)
Infectious disease	14 (10)	11 (8)	3 (2)	44 (7.71)
Pneumonia and other pulmonary	18 (12)	14 (10)	4 (3)	49 (8.82)
Other natural causes	23 (16)	16 (11)	7 (5)	49 (11.51)
Other external causes	12 (8)	11 (8)	1 (1)	38 (8.53)
Total underlying causes of death	146	105 (72)	41 (28)	43 (9.85)

The association between alcohol and mortality (both overdose and hepatic disease) fits within the current body of knowledge. Alcohol, the most commonly detected concomitant substance in opioid-related deaths (along with benzodiazepines), potentiates the respiratory depressant effect of heroin and other opioids. Thus, concomitant use may well prove fatal by overdose, due to this interaction (Darke et al., 2000). Alcohol abuse is also strongly associated with methadone-related deaths (NTA, 2007). Chronic HCV (Hepatitis C Virus) is a major cause of liver cirrhosis, as is alcohol misuse (McCartney and Beard, 2010; Menon et al., 2001). HCV occurs at rates between 40% and 90% in injecting drug users (Limburg, 2004) and the combined effect of HCV and alcohol consumption is deleterious for liver disease. The risk for developing cirrhosis in patients who are HCV-positive and abuse alcohol is 147 times higher than HCV-positive patients who abstain (Poynard et al., 1997). Comorbid AUD in OUD patients, therefore, presents particular challenges for clinicians; for example how best to respond to clients who are under the influence of alcohol when presenting for their medication? There is little research evidence to guide the clinician as to how best to respond to these circumstances (NTA, 2009) and, given the heightened mortality rates in this group, more research and guidance is urgently needed.

Current research in PD and OUD reports that screening positively for a borderline personality disorder (BPD) was a risk factor for suicide attempts in heroin-using population (Maloney et al., 2007) and highlighted the importance of assessing impulsivity and psychiatric comorbidity when determining risk factors for suicidal behaviour (Maloney et al., 2009). Our study investigated mortality

Table 6
Competing risk regression analyses of factors associated with cause-specific mortality in opioid-dependent individuals in fully adjusted model.

	Fully adj. SHR for overdose mortality (95%CI)*	Fully adj. SHR for alcoholic and other liver disease mortality (95%CI)*	Fully adj. SHR for all other causes of mortality (95%CI)*
Psychological well-being			
Psychological health status	1.02 (0.92–1.13)	1.01 (0.93–1.10)	1.02 (0.95–1.10)
Comorbid serious mental illness			
Not present	Referent	Referent	Referent
Present	0.75 (0.15–3.76)	0.30 (0.05–1.97)	0.46 (0.10–2.18)
Comorbid personality disorder			
Not present	Referent	Referent	Referent
Present	1.34 (0.38–4.71)	**3.82 (1.40–10.46)**	2.11 (0.68–6.53)
Comorbid alcohol use disorder			
Not present	Referent	Referent	Referent
Present	**2.53 (1.14–5.61)**	**7.28 (2.65–19.97)**	0.89 (0.44–1.81)

* Adjusted for sociodemographic factors, severity of drug use, risk behaviours and physical health (see Table 3 for full list of confounders).
Statistically significant ($p < 0.05$) subdistribution hazard ratios (SHR) are in bold.

risk beyond suicide. The independent association of comorbid PD, with all-cause and liver-disease mortality might reflect the cumulative influences of a more chaotic lifestyle, such as engagement in risk behaviours, alcohol use, difficulties forming stable relationships, impulsivity, and less treatable addiction. It is possible that either the use of opioids is especially harmful for individuals with PD, or the use of heroin or other opioids might aggravate a pre-existing PD. Alternatively, OUDs and some PDs may be tautological (Rounsaville et al., 1998). Such results should, however, be interpreted with caution. Antisocial Personality Disorder for example, is a particularly problematic diagnosis for drug users. An illicit opioid user, for instance, will have a high chance of qualifying for the diagnosis due to their illicit drug use, regardless of whether they actually have a PD, creating additional challenges to the treatment providers. Nonetheless, only a small proportion of dual-diagnosis patients actually receive treatment for both PD and OUD disorders (SAMHSA, 2012). Patients with co-occurring disorders can face challenges accessing treatment, as they may be excluded from mental health services if they admit to a substance abuse problem, and vice versa (SAMHSA, 2012).

We did not find a significant association between mortality and psychological health rating—a reliable measure of indication for problems with anxiety, depressive symptoms and other emotional problems (Marsden et al., 2008). Previous literature focusing on the impact of depression and anxiety in opioid users is also mixed; one study found that higher levels of anxiety have been associated with mortality (Gossop et al., 2002), whereas other found no such association (Arendt et al., 2011). Although studies have consistently shown that between a quarter and a third of heroin users meet the criteria for a life-time diagnosis of major depression (Darke and Ross, 1997; Dinwiddie et al., 1992), we did not see this in our sample—only 3.5% of the cohort received ICD10 diagnosis of a depressive disorder. This low proportion of comorbid depressive disorders may result from (a) tendency to under-diagnose depression in people with OUD perhaps because services focus more on the primary OUD diagnosis and/or diagnoses which are deemed to be more life threatening, (b) often mood disorder may improve with effective management of the addiction and (c) reluctance to make a diagnosis which might lead to prescription of another psychotropic medication.

This study has a number of strengths. SLaM is a large provider of secondary mental healthcare in Europe, with close to 100% monopoly provision to its geographic catchment. We were thus able to draw on electronic addictions service clinical records of almost five thousand OUD patients providing the statistical power to simultaneously control for a range of potential confounders. SLaM patient death-tracing is regularly updated and is based on death certificates issued across the UK for both active and non-active SLaM patients. Furthermore, we were able to determine 83% of underlying causes of death for this cohort by linking our SLAM data with external Office of National Statistics (ONS) data, which include those derived from coroner's reports. Nevertheless, the results of this study need to be considered with caution, in light of certain limitations. This is an observational study and residual confounding is possible. Our potential confounders included deprivation score rather than a direct measure to socio-economic status. Our measure of physical health is a single and self-reported measure, which does not capture all possible physical diseases. It should be noted that mean age at ICD10-F11 diagnosis was 37.5 years old, which does not reflect the "classic-profile" of heroin/opioid addict who will first approach services in their early or mid-20s. This is because our data were limited to diagnosis given within the observation period, therefore may not reflect a true representative of age at *first* OUD diagnosis, which may have been given in treatment episodes prior to the start of our analytical period. We were able to establish causes of mortality based on ONS linked data; however, we could not differentiate between intentional (i.e., suicide) and non-intentional (i.e., accidental) overdoses. Furthermore, SLaM is a secondary service provider, and the sample would not have included heroin users within the community who are not known to addictions services or who seek help privately. The generalizability of findings is therefore to specialist secondary care services. Finally, our indicator for depression and anxiety was based on a subjective psychological health status rating and not a clinical diagnosis. We chose this measure because of the low numbers with an ICD-10 depression diagnosis in the cohort.

Despite our large cohort, the number of deaths within those with SMI comorbidity was small and important effects might have been missed. Future research should explore these associations further using larger samples. Similarly, our relatively small OUD + PD sample put limits on power for further and more detailed analysis. To aid in our understanding of mortality risk in this group, further research should focus on differences in personality clusters, and with a particular focus on directions of casualty (i.e., longitudinal analysis). Furthermore, our inclusion criteria included date of OUD and having seen a clinician at least once during the observation period, therefore we were not able to explore associations with mortality by frequency of clinician contact to establish possible differences in hazard rations for persons with the minimum criteria for inclusion compared to those with frequent regularity and clinician contact during the study timeframe. This, also, is a worthwhile research target.

Our findings carry important implications for clinicians, researchers and service providers. Our results suggest among people with OUD, a patient group with an already substantially elevated risk of premature mortality, the presence of co-morbid PD and/or AUD puts these individuals at even greater risk. This marked observation should prompt a change of practice for clinicians but also for those responsible for defining and purchasing health care services. Existing treatments for OUD are already known to reduce mortality (Cornish et al., 2010) and that the treatment being delivered influences the resulting long-term mortality (Faggiano et al., 2003). Correctly tailored treatment is therefore even more important when AUD or PD co-exist with the OUD. Additionally, specific anti-overdose harm reduction measures such as overdose training for family and peers in overdose management (Williams et al., 2014) and pre-provision of emergency naloxone (Strang et al., 2008) should be provided and would save lives. This study highlights the importance of assessment for PD and AUD in OUD patients in order to identify individuals at substantially elevated mortality risk to enable a more personalized approach to their medical care.

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Contributions

All the authors listed contributed to the process of hypothesis generation, data collection, statistical analyses, or manuscript preparation, and fulfilled the criteria for authorship. Additionally, KMB wrote the manuscript and analyzed data. RDH and JS were primary supervisors. RS and MH were responsible for securing funding for CRIS and constituent studies. SLH (and all other authors) provided their suggestions during the manuscript review process. MB is responsible for technical oversight of CRIS.

Conflict of interest

RH, MB and RS have received research funding from Roche, Pfizer, J&J and Lundbeck. JS has conducted a variety of research studies of addictive disorders and treatments and has provided consultancy to, and is currently seeking funding from, pharmaceutical companies considering development of more suitable treatments (none was the subject of study in this work). Other authors have no conflict of interest.

References

Arendt, M., Munk-Jorgensen, P., Sher, L., Jensen, S.O., 2011. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment. Drug Alcohol Depend. 114, 134–139, http://dx.doi.org/10.1016/j.drugalcdep.2010.09.013.

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., Munk-Jorgensen, P., 2007. Psychopathology among cannabis-dependent treatment seekers and association with later substance abuse treatment. J. Subst. Abuse Treat. 32, 113–119, http://dx.doi.org/10.1016/j.jsat.2006.07.005.

Bargagli, A.M., Hickman, M., Davoli, M., Perucci, C.A., Schifano, P., Buster, M., Brugal, T., Vicente, J., COSMO European Group, 2006. Drug-related mortality and its impact on adult mortality in eight European countries. Eur. J. Public Health 16, 198–202, http://dx.doi.org/10.1093/eurpub/cki168.

Brooner, R.K., King, V.L., Kidorf, M., Schmidt Jr., C.W., Bigelow, G.E., 1997. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. Arch. Gen. Psychiatry 54, 71–80.

Cacciola, J.S., Alterman, A.I., Rutherford, M.J., McKay, J.R., Mulvaney, F.D., 2001. The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. Drug Alcohol Depend. 61, 271–280.

Chang, C.K., Hayes, R.D., Broadbent, M., Fernandes, A.C., Lee, W., Hotopf, M., Stewart, R., 2010. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry 10, 77, http://dx.doi.org/10.1186/1471-244x-10-77.

Cornish, R.M.J., Strang, J., Vickerman, P., Hickman, M., 2010. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ, http://dx.doi.org/10.1136/bmj.c5475.

Cox, D.R., 1972. Regression models and life-ables. J. R. Stat. Soc. 34, 187–220.

Darke, S., Hall, W., Swift, W., 1994. Prevalence, symptoms and correlates of antisocial personality disorder among methadone maintenance clients. Drug Alcohol Depend. 34, 253–257.

Darke, S., Ross, J., 1997. Polydrug dependence and psychiatric comorbidity among heroin injectors. Drug Alcohol Depend. 48, 135–141.

Darke, S., Ross, J., 2002. Suicide among heroin users: rates, risk factors and methods. Addiction 97, 1383–1394.

Darke, S., Ross, J.E., Zador, D., Sunjic, S., 2000. Heroin-related deaths in New South Wales, 1992–96. Drug Alcohol Depend. 60, 141–150.

Davoli, M., Perucci, C.A., Forastiere, F., Doyle, P., Rapiti, E., Zaccarelli, M., Abeni, D.D., 1993. Risk factors for overdose mortality: a case-control study within a cohort of intravenous drug users. Int. J. Epidemiol. 22, 273–277.

Dickey, B., Dembling, B., Azeni, H., Normand, S.L., 2004. Externally caused deaths for adults with substance use and mental disorders. J. Behav. Health Serv. Res. 31, 75–85.

Dinwiddie, S.H., Reich, T., Cloninger, C.R., 1992. Psychiatric comorbidity and suicidality among intravenous drug users. J. Clin. Psychiatry 53, 364–369.

Disney, E., Kidorf, M., Kolodner, K., King, V., Peirce, J., Beilenson, P., Brooner, R.K., 2006. Psychiatric comorbidity is associated with drug use and HIV risk in syringe exchange participants. J. Nerv. Ment. Dis. 194, 577–583, http://dx.doi.org/10.1097/01.nmd.0000230396.17230.28.

Faggiano, F., Vigna-Taglianti, F., Versino, E., Lemma, P., 2003. Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst. Rev., Cd002208, http://dx.doi.org/10.1002/14651858.cd002208.

Fok, M.L., Hayes, R.D., Chang, C.K., Stewart, R., Callard, F.J., Moran, P., 2012. Life expectancy at birth and all-cause mortality among people with personality disorder. J. Psychosom. Res. 73, 104–107, http://dx.doi.org/10.1016/j.jpsychores.2012.05.001.

Ghodse, A.H., Sheehan, M., Taylor, C., Edwards, G., 1985. Deaths of drug addicts in the United Kingdom 1967–81. Br. Med. J. Clin. Res. Ed. 290, 425–428.

Gossop, M., Marsden, J., Stewart, D., 2001. NTORS After Five Years (National Treatment Outcome Research Study): Changes In Substance Use, Health And Criminal Behaviour In The Five Years After Intake. National Addiction Centre, London.

Gossop, M., Stewart, D., Treacy, S., Marsden, J., 2002. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. Addiction 97, 39–47.

Harris, E.C., Barraclough, B., 1998. Excess mortality of mental disorder. Br. J. Psychiatry 173, 11–53.

Hayes, R.D., Chang, C.K., Fernandes, A., Begum, A., To, D., Broadbent, M., Hotopf, M., Stewart, R., 2012. Associations between symptoms and all-cause mortality in individuals with serious mental illness. J. Psychosom. Res. 72, 114–119, http://dx.doi.org/10.1016/j.jpsychores.2011.09.012.

Hayes, R.D., Chang, C.K., Fernandes, A., Broadbent, M., Lee, W., Hotopf, M., Stewart, R., 2011. Associations between substance use disorder sub-groups, life expectancy and all-cause mortality in a large British specialist mental healthcare service. Drug Alcohol Depend. 118, 56–61, http://dx.doi.org/10.1016/j.drugalcdep.2011.02.021.

Khantzian, E.J., Treece, C., 1985. DSM-III psychiatric diagnosis of narcotic addicts. Recent findings. Arch. Gen. Psychiatry 42, 1067–1071.

King, V.L., Kidorf, M.S., Stoller, K.B., Brooner, R.K., 2000. Influence of psychiatric comorbidity on HIV risk behaviors: changes during drug abuse treatment. J. Addict. Dis. 19, 65–83, http://dx.doi.org/10.1300/J069v19n04_07.

Krausz, M., Verthein, U., Degkwitz, P., 1999. Psychiatric comorbidity in opiate addicts. Eur. Addict. Res. 5, 55–62, DOI 18966.

Landheim, A.S., Bakken, K., Vaglum, P., 2006. Impact of comorbid psychiatric disorders on the outcome of substance abusers: a six year prospective follow-up in two Norwegian counties. BMC Psychiatry 6, 44, http://dx.doi.org/10.1186/1471-244x-6-44.

Limburg, W., 2004. Natural history, treatment and prevention of hepatitis C in injecting drug users: an overview. In: Jager, J.C., Limburg, W., Kretzschmar, M., Postma, M.J., Wiessing, L. (Eds.), Hepatitis C And Injecting Drug Use: Impact, Costs And Policy Options. European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

Maloney, E., Degenhardt, L., Darke, S., Mattick, R.P., Nelson, E., 2007. Suicidal behaviour and associated risk factors among opioid-dependent individuals: a case-control study. Addiction 102, 1933–1941, http://dx.doi.org/10.1111/j. 1360-0443.2007.01971.x.

Maloney, E., Degenhardt, L., Darke, S., Nelson, E.C., 2009. Impulsivity and borderline personality as risk factors for suicide attempts among opioid-dependent individuals. Psychiatry Res. 169, 16–21, http://dx.doi.org/10.1016/j.psychres.2008.06.026.

Marsden, J., Farrell, M., Bradbury, C., Dale-Perera, A., Eastwood, B., Roxburgh, M., Taylor, S., 2008. Development of the treatment outcomes profile. Addiction 103, 1450–1460, http://dx.doi.org/10.1111/j. 1360-0443.2008.02284.x.

Mason, B.J., Kocsis, J.H., Melia, D., Khuri, E.T., Sweeney, J., Wells, A., Borg, L., Millman, R.B., Kreek, M.J., 1998. Psychiatric comorbidity in methadone maintained patients. J. Addict. Dis. 17, 75–89, http://dx.doi.org/10.1300/J069v17n03_07.

Mattisson, C., Bogren, M., Ojehagen, A., Nordstrom, G., Horstmann, V., 2011. Mortality in alcohol use disorder in the Lundby Community Cohort—a 50 year follow-up. Drug Alcohol Depend. 118, 141–147, http://dx.doi.org/10.1016/j.drugalcdep.2011.03.008.

McCartney, E.M., Beard, M.R., 2010. Impact of alcohol on hepatitis C virus replication and interferon signaling. World J. Gastroenterol. 16, 1337–1343.

Menon, K.V., Gores, G.J., Shah, V.H., 2001. Pathogenesis, diagnosis, and treatment of alcoholic liver disease. Mayo Clin. Proc. 76, 1021–1029, http://dx.doi.org/10.4065/76.10.1021.

National Treatment Agency for Substance Misuse (NTA), 2007. Study To Determine The Relationship Between Blood-Heroin/Methadone And Concomitant Drug Levels In Fatal Opioid Poisonings. NTA, ⟨http://www.nta.nhs.uk⟩.

National Treatment Agency for Substance Misuse (NTA), 2009. Towards Successful Treatment Completion: A Good Practice Guide. Effective Treatment Changing Lives. NTA, ⟨http://www.nta.nhs.uk⟩.

Office for National Statistics (ONS), 2009. Mortality Statistics, Deaths Registered in 2008. ONS.

Poynard, T., Bedossa, P., Opolon, P., 1997. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 349, 825–832.

Robins, L.N., Regier, D.A., 1991. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. Free Press, New York, NY.

Rodriguez-Llera, M.C., Domingo-Salvany, A., Brugal, M.T., Silva, T.C., Sanchez-Niubo, A., Torrens, M., 2006. Psychiatric comorbidity in young heroin users. Drug Alcohol Depend. 84, 48–55, http://dx.doi.org/10.1016/j.drugalcdep.2005.11.025.

Rounsaville, B.J., Kosten, T.R., Weissman, M.M., Kleber, H.D., 1986. Prognostic significance of psychopathology in treated opiate addicts. A 2.5-year follow-up study. Arch. Gen. Psychiatry 43, 739–745.

Rounsaville, B.J., Kranzler, H.R., Ball, S., Tennen, H., Poling, J., Triffleman, E., 1998. Personality disorders in substance abusers: relation to substance use. J. Nerv. Ment. Dis. 186, 87–95.

Rounsaville, B.J., Weissman, M.M., Kleber, H., Wilber, C., 1982. Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch. Gen. Psychiatry 39, 161–168.

Substance Abuse and Mental Health Services Administration (SAMHSA), 2012. Results from the 2011 National Survey on Drug Use and Health: Mental Health Findings. In: NSDUH Series H-45. From Substance Abuse and

Mental Health Services Administration, ⟨http://www.samhsa.gov/data/NSDUH/2k11MH_FindingsandDetTables/2K11MHFR/NSDUHmhfr2011.htm⟩.
Shah, N.G., Lathrop, S.L., Reichard, R.R., Landen, M.G., 2008. Unintentional drug overdose death trends in New Mexico, USA, 1990–2005: combinations of heroin, cocaine, prescription opioids and alcohol. Addiction 103, 126–136, http://dx.doi.org/10.1111/j. 1360-0443.2007.02054.x.
Stewart, R., Soremekun, M., Perera, G., Broadbent, M., Callard, F., Denis, M., Hotopf, M., Thornicroft, G., Lovestone, S., 2009. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 9, 51, http://dx.doi.org/10.1186/1471-244x-9-51.
Strang, J., Manning, V., Mayet, S., Best, D., Titherington, E., Santana, L., Offor, E., Semmler, C., 2008. Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. Addiction 103, 1648–1657, http://dx.doi.org/10.1111/j. 1360-0443.2008.02314.x.
Weaver, T., Madden, P., Charles, V., Stimson, G., Renton, A., Tyrer, P., Barnes, T., Bench, C., Middleton, H., Wright, N., Paterson, S., Shanahan, W., Selvewright, N., Ford, C., Comorbidity of Substance Misuse and Mental Illness Collaborative Study Team, 2003. Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. Br. J. Psychiatry 183, 304–313.
World Health Organisation (WHO), 1993. The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic Criteria for Research. WHO, Geneva.
Williams, A.V., Marsden, J., Strang, J., 2014. Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction 109, 250–259, http://dx.doi.org/10.1111/add.12360.

(iv) Published abstract (Chapter 4)

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YOKOHAMA, JAPAN

OR03-4

PSYCHIATRIC COMORBIDITY AND EXCESS ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY IN OPIOID ADDICTS

K. M. Bogdanowicz[1], R. Stewart[2], M. Broadbent[3], S. L. Hatch[2], M. Hotopf[2], J. Strang[1] and R. Hayes[2]
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Introduction. The challenge of personalised medicine is to identify components of addiction that are relevant to an individual in a way that treatment and drug overdose preventions can be tailored. Opioid misusers continue to have recognised extremely high mortality but the influence of psychiatric comorbidity in excess all-cause and cause-specific mortality is questionable.
Methods. Opioid-dependent (OD) patients were identified in London-based patient register, which contains records on over 220,000 cases linked to national mortality tracing. We used Cox regression to model the effect of psychiatric co-morbidity on mortality, controlling for a broad range of potential confounders.
Results. We identified 4837 OD patients with 176 deaths. The presence of comorbid personality disorder (PD) and alcohol use disorder (AUD) was found to be associated with increased all-cause mortality in all models, including the fully adjusted model. AUD was associated with two-fold increased risk of fatal overdose and seven-fold risk for liver-related deaths. Individuals with OUD and comorbid PD had almost four-times greater risk of liver related deaths compared to those without PD.
Conclusions. The study highlights the importance of assessment for PD and alcohol misuse among opioid addicts in order to identify individuals at substantially elevated mortality risk for a more personalised approach to their medical care.This research is part of a larger project, which focusses on electronic-based personalised medicine in drug addiction. The complete research plan as well as research October '14 research update will also be provided.

(v) Example of data extraction plan, used for analysis in Chapter 5.

Currency/Measure	Patient
Window start date	01.04.2008
Window end date	31.03.2014 (we will re-run when new cause of death comes in)
Dataset filter criteria	F11* (primary and secondary patients (via CRIS and GATE) diagnosed within the 01-04.2008 - 31.03.2014 window with at least one item on the "BRSA-A" form completed within 1st June 2008 and window end date.

PROJECT: Brief Risk Assessment Addictions (BRAA) - March '15

brcid	Brief Risk Screen Addictions (BRAS-A)	BRSA-A Date	F11 Diagnosis date	date of birth	date of death	cause of death	gender	ethnicity	dep score	Admissions	Admission s CAG type	Buprenorphine	Methadone	Suboxone	Naloxone
	Brief Risk Assessment Addictions. Please extract first BRAA form for each patient completed between 01.06.2008 and the window end. Please extract all BRAA items including Null values within form. I would also like to know the % of F11 patients within the window who did not have BRAA assessment done at all. I just need the %.	Please provide date of given BRAA assessment	Please provide F11 diagnosis date within 01.04.2008-31.03.2014 window.		if applicable, please provide DoD	if applicable, please provide ICD10 underlying cause of death			Please specify deprivation score closest but prior* to the date of extracted BRAA form. If >35% NULL value, then please provide score closest to extracted BRAA (incl. closest	Please specify the total number of admissions seperately for Addictions CAG, Mood-anxiety-&-personality CAG; Psych.med CAG; and Psychosis CAG.	Please specify the total number of admissions seperately for Addictions CAG, Mood-anxiety-&-personality CAG; Psych.med CAG; and Psychosis CAG.	In a binary variable please advise if buprenorphine was prescribed within a period of 2 months after BRAA assessment.	In a binary variable please advise methadone was prescribed within a period of 2 months after BRAA assessment.	In a binary variable please advise suboxone was prescribed within a period of 2 months after BRAA assessment.	In a binary variable please advise naloxone was prescribed within a period of 2 months after BRAA assessment. Please also search events for notes for "naloxone training" &...

(vi) Treatment Outcomes Profile (TOP) (Marsden et al., 2008)

Treatment Outcomes Profile

Name of client | D.O.B. (dd/mm/yyyy) | Name of keyworker

TOP interview date (dd/mm/yyyy) | Gender: M ☐ F ☐ | Treatment stage: Modality start ☐ Care plan review ☐ Discharge ☐ Post-discharge ☐

Section 1: Substance use

Record the average amount on a using day and number of days substances used in each of past four weeks

	Average		Week 4		Week 3		Week 2		Week 1		Total	
a Alcohol		units/day		0–7		0–7		0–7		0–7		0–28
b Opiates		g/day		0–7		0–7		0–7		0–7		0–28
c Crack		g/day		0–7		0–7		0–7		0–7		0–28
d Cocaine		g/day		0–7		0–7		0–7		0–7		0–28
e Amphetamines		g/day		0–7		0–7		0–7		0–7		0–28
f Cannabis		spliff/day		0–7		0–7		0–7		0–7		0–28
g Other problem substance?		g/day		0–7		0–7		0–7		0–7		0–28

Name.....

Section 2: Injecting risk behaviour

Record number of days client injected non-prescribed drugs in past four weeks (if no, enter zero and go to section 3)

	Week 4		Week 3		Week 2		Week 1		Total	
a Injected		0–7		0–7		0–7		0–7		0–28

b Inject with needle or syringe used by someone else? Yes ☐ No ☐

c Inject using a spoon, water or filter used by someone else? Yes ☐ No ☐

Enter 'Y' if any yes, otherwise 'N'

Section 3: Crime

Record days of shoplifting, drug selling and other categories committed in past four weeks

	Week 4		Week 3		Week 2		Week 1		Total	
a Shoplifting		0–7		0–7		0–7		0–7		0–28
b Drug selling		0–7		0–7		0–7		0–7		0–28

c Theft from or of a vehicle Yes ☐ No ☐

d Other property theft or burglary Yes ☐ No ☐

e Fraud, forgery and handling stolen goods Yes ☐ No ☐

Enter 'Y' if any yes, otherwise 'N'

f Committing assault or violence Yes ☐ No ☐ Enter 'Y' or 'N'

Section 4: Health and social functioning

a Client's rating of psychological health status (anxiety, depression and problem emotions and feelings)

Poor 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 **Good** 0–20

Record days worked and at college or school for the past four weeks

	Week 4		Week 3		Week 2		Week 1		Total	
b Days paid work		0–7		0–7		0–7		0–7		0–28
c Days attended college or school		0–7		0–7		0–7		0–7		0–28

d Client's rating of physical health status (extent of physical symptoms and bothered by illness)

Poor 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 **Good** 0–20

Record accommodation items for the past four weeks

e Acute housing problem Yes ☐ No ☐ Enter 'Y' or 'N'

f At risk of eviction Yes ☐ No ☐ Enter 'Y' or 'N'

g Client's rating of overall quality of life (e.g. able to enjoy life, gets on well with family and partner)

Poor 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 **Good** 0–20

TOP v1.0 May 2007

(vii.) KCL ethics approval for technical appraisal qualitative study (see Chapter 8 for details)

Research Ethics
Office

Franklin Wilkins Building
5.9 Waterloo Bridge Wing
Waterloo Road
London SE1 9NH
Telephone 020 7848 4020/4070/4077
rec@kcl.ac.uk

KING'S College LONDON

Karolina Bogdanowicz

12 June 2015

Dear Karolina Magda ,

Study Title: Personalised Risk Profile Alerts in Opioid Dependency: Consultation and Technical Appraisal

Study Reference: LRS-14/15-0832

I am pleased to inform you that full approval for your project has been granted by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information, ethical approval is granted until 12th June 2018. If you need approval beyond this point, you will need to apply for an extension at least two weeks before this. You will be required to explain the reasons for the extension. However, you will not need to submit a full re-application unless the protocol has changed. If you have been granted approval for only 12 months, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the data-collection phase of the study. This will be until the date specified in this letter. However, you do not need ethical approval to cover subsequent data analysis or publication of the results.

For secondary data-analysis, ethical approval is applicable to the data that is sensitive or identifies participants.

Approval is applicable to period in which such data is accessed or evaluated.

Please note you are required to adhere to all research data/records management and storage procedures agreed to as part of your application. This will be expected even after the completion of the study.

If you do not start the project within three months of this letter, please contact the Research Ethics Office.

Please note that you will be required to obtain approval to modify the study. This also encompasses extensions to periods of approval. Please refer to the URL below for further guidance about the process:

http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact the Research Ethics Office:

(http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx)

We wish you every success with this work.

Yours sincerely,

James Patterson - Senior Research Ethics Officer

For and on behalf of

Professor Gareth Barker, Chair

PNM RESC

Cc: Richard Hayes